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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

OF THE

MEDICAL DEVICES ADVISORY COMMITTEE

Thursday, January 16, 1997

9:20 a.m.

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507 C Street, N.E.
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at

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Rockville, Maryland

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at

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Mary Cornelius, Executive Secretary

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John H. Sadler, M.D.

FDA

Robert Gatling, Jr.

at

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P R O C E E D I N G S

DR. MELMAN: I would like to call the meeting to order. I would like to remind everyone in attendance at this meeting that you are requested to sign in on the attendance sheet at the doors. I would like to note for the record that the voting members constitute a quorum as required by 21CFR, Part 14.

In addition, Dr. Robert DiLoreto, who was supposed to be here, could not be here because his plane was canceled because of snow in Detroit. But he is on the telephone, on the speakerphone, and he is listening to everything you say and will participate later on via the telephone.

I would like every member to introduce him or herself, to designate their specialty, position, title, institution and status on the panel; that is, either a voting member, a consultant. I will start on my far right, which would be Dr. Bennett.

DR. BENNETT: Alan Bennett. I am Vice President of Medical Affairs, C.R. Bard. I am a retired urologist.

DR. JONES: Dr. George W. Jones. I am a retired urologist also but I am Chairman of Prostate Cancer for the

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College of Surgeons, American Cancer Society, on the international committee. I am Professor of Urology, still, at Howard.

MR. GATLING: I am Bob Gatling. I am an Associate Division Director here at FDA.

DR. HUNTER: I am Pat Hunter, Clinical Assistant Professor at the University of Florida and a practicing urologist.

DR. JETER: I am Katherine Jeter. I am the retired Executive Director of the National Association for Continence and I am the consumer representative.

DR. SADLER: I am John Sadler. I am a nephrologist from Baltimore. I am on the faculty at the University of Maryland.

DR. MELMAN: I am Arnold Melman. I am Professor and Chairman of Urology at Albert Einstein College of Medicine, a working urologist.

MS. CORNELIUS: Good morning. I am Mary Cornelius, Executive Secretary of the Gastroenterology and Urology Devices Advisory Panel.

Before I begin, I would like to read a statement

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concerning the appointment to temporary voting status.

Pursuant to the authority granted under the Medical Advise Advisory Committee Charter dated October 27, 1990, as amended April 20, 1995, Dr. Robert DiLoreto, Dr. Patrick Hunter, Dr. John Sadler have been appointed as voting members by Dr. Bruce Burlington, Director for the Center for Devices and Radiological Health for the January 16, 1997 meeting of the Gastroenterology and Urology Devices Panel.

For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone customary conflict of interest review and they have reviewed the material to be considered at this meeting.

The FDA is concerned about conflict of interest. The following announcement addresses the conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests

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reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

Full waivers have been granted to Dr. Leonard Vertuno, who could not make it today, Dr. Katherine Jeter, Dr. Robert DiLoreto and Dr. Patrick Hunter for their financial interests in firms that could potentially be affected by the committee's deliberations.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15, of the Parklawn Building.

We would also like to note for the record that the Agency took into consideration other matters regarding Dr. Arnold Melman and Dr. Hunter. Both Dr. Melman and Dr. Hunter reported involvement with firms at issue on matters not related to the PMA supplement being discussed today.

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Therefore, the Agency has determined that both individuals may participate fully in the panel's deliberations.

In the event that discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial interest, the participants should exclude themselves from such involvement and their exclusion shall be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

If anyone has anything to discuss concerning these matters, please advise me now and we can leave the room to discuss them.

FDA also has a conflict of interest policy regarding persons making public statements at advisory panel meetings. Dr. Melman will ask all persons making statements either during the open public meeting or during the open committee meeting discussion portions of the meeting to state their name, professional affiliation and disclose

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whether they have any financial interest in any medical device company.

The following is a definition of financial interest in the sponsor company. First, compensation for time and services of clinical investigators, their assistants and staff, in conducting the studies and appearing at the panel on behalf of the application; second, a direct stake in the product under review, such as an inventor of the product, a patent holder or owner of shares of stock; and, third, owner or part owner of the company. No statement, of course, is required from employees of the company.

FDA seeks communication with industry and the clinical community in a number of different ways. First, FDA welcomes and encourages premeetings with sponsors prior to all IDE and PMA submissions. This affords the sponsor an opportunity to discuss issues that could impact the review process. Second, the FDA communicates through the use of guidance documents.

Toward this end, FDA develops two types of guidance documents for manufacturers to follow when

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submitting a premarket application. One type is simply a summary of the information that has historically been requested on devices that are well understood in order to determine substantial equivalence.

The second type of guidance is one that develops as we learn about new technology. FDA welcomes and encourages the panel and industry to provide comments concerning our guidance documents. A copy of the revisions to the draft guidance on penile rigidity implants and a list of all GU panel guidance documents that can be obtained through DSMA are available at the door.

Finally, I would like to remind you that the tentative dates of the panel meetings scheduled for 1997 are: May 1 and 2, August 6 and 7, November 6 and 7.

Open Public Hearing

DR. MELMAN: We will now proceed with the open public hearing session of the meeting scheduled for one hour. I would like to ask at this time that all persons addressing the panel come forward to the microphone and speak clearly as the transcriptionist is dependent upon this means of providing an accurate transcription of the

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proceedings of the meeting.

Before making your presentation to the panel, state your name and affiliation and the nature of your financial interest in the company. Let me quickly remind you that you that the definition of financial interest in the sponsor company may include: compensation for time and services of clinical investigators, their assistants and staff, in conducting the study and in appearing at the panel meeting on behalf of the applicant; direct stake in the product under review--for example, an inventor of the product, patent holder, owner of shares of stock, et cetera; an owner or part owner of a company. No statement is necessary from employees of that company.

Anyone in the audience wishing to address the audience, would you please raise your hand and you may have an opportunity to speak.

Open Committee Discussion

DR. MELMAN: Since there are no requests noted, we will now proceed to the open committee discussion. I would like to remind public observers that this portion of the meeting is open to public observation. Public attendees may

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not participate except at the specific request of the panel.

We will begin the open committee discussion with an information update from the FDA. The first speaker is Dr. John Baxley.

FDA Presentation

Update on PMAs: Liposorber LA-15 System

Lipoprotein Precipitation, (H.E.L.P.) System

MR. BAXLEY: Good morning.

[Slide.]

I am John Baxley, a medical engineer and scientific reviewer in FDA's Urology and Lithotripsy Devices Branch. The purpose of my presentation this morning is to update the panel on FDA's guidance for the content of premarket notifications or 510(k) submissions for penile rigidity implants.

This group of devices refers to the various types of non-inflatable penile implants that are on the market such as malleable or hinged prostheses.

[Slide.]

First, let me provide a brief history regarding the Agency's regulation of these devices. Penile rigidity

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implants are pre-Amendments or pre-1976 devices and were classified by FDA in 1983 into Class III. As a result, these devices have been reviewed under the 510(k) process where clearance is based on a demonstration of substantial equivalence to an existing device.

In August of 1995, FDA published in the Federal Register a list of pre-Amendments Class III devices which we believe are good candidates for reclassification into Class II. Penile rigidity implants were included on that list.

As specified in the statute, reclassification to Class II requires the identification of special controls which are device-specific requirements intended to minimize the risks of the device. Our intent is that this guidance document contains all the special controls necessary to insure that risks of penile rigidity implants are sufficiently reduced.

This guidance document was originally prepared in May, 1995. The content of this document was primarily based on the types of information routinely requested and past 510(k)s for penile rigidity implants. At the same time, however, we also tried to anticipate the future special

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controls that would be necessary in the event that we proceed with reclassification.

[Slide.]

This past December, we revised the guidance document based on our review of industry 515(i) submissions of safety and effectiveness data. Manufacturers of penile rigidity implants submitted these documents as part of a process to assist FDA in reclassifying these devices.

These industry submissions identified several additional special controls for penile rigidity implants which we believe should be incorporated into our guidance document. These additional items generally involve additions to our recommendations for physician and patient labeling with the content of the other sections remaining the same.

In addition to these additional labeling recommendations, we also took the opportunity to update the guidance document where needed such as referencing the proposal to downclassify the devices to Class II and updating several citations to other FDA documents.

[Slide.]

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Listed on the overhead are the general sections of the guidance document. First, we request that manufacturers provide a description of the device's design and intended use. Next is a section outlining the recommendations for biocompatability testing which are consistent with the ODE Blue Book regarding the use of the ISO standard.

Third is to evaluate the tendency of a device to mechanically fail. The guidance document includes a section on the recommended mechanical reliability test for new penile-rigidity implants. As summarized in the document, these tests include fatigue testing, rigidity, positioning and concealability testing, buckling testing and joint strength testing.

[Slide.]

For novel device designs, we recommend that the manufacturers submit the results of clinical testing to verify device equivalence. Clinical testing is not requested for routine 510(k)s or existing device designs. Rather, such information would only be requested for those devices that are significantly different in design, materials, control method, operating principle or intended

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use.

For these innovative devices, the guidance document recommends a six-month study to assess short-term safety and effectiveness outcomes for comparison to an existing device.

Next, the sterilization information recommended in the guidance document is similar to what is typically required for any sterile device such as a description of the sterilization process and validation method.

Lastly, the guidance document makes general and specific recommendations regarding the content of both physician and patient labeling. This is a major part of the document which we believe is essential for reducing many of the device's risks.

[Slide.]

Let me briefly present the kinds of labeling information that the guidance document recommends beginning with the physician labeling. The guidance document recommends including instructions to give prospective patients the patient labeling prior to surgery, a description of all device risks including factors or

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practices that may increase the incidence of each risk so patients are aware of the types of complications that can occur, and instructions for the physician to counsel patients on the healing process so patients can better differentiate between routine symptoms and those which require medical attention.

[Slide.]

We also recommend that the physician labeling state that penile rigidity implants are subject to wear and therefore should not be considered lifetime implants so patients realize prior to device implantation that there is a possibility of implant failure and reoperation and to include instructions regarding implant handling, patient preparation, surgical technique and post-operative care.

These physician instructions provide guidance on how to minimize the incidence of intraoperative complications such as the use of sterile technique and patient preparation to reduce the risk of infection, careful surgical technique to minimize the risks of erosion, migration and extrusion, and proper implant handling to reduce the chance of damaging the device.

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[Slide.]

Regarding the patient labeling, the guidance document recommends that manufacturers include a description of all device risks including factors or practices that may increase the incidence of each risk, information on how these risks can be identified and treated, to help patients know when to seek medical attention, and information regarding the expected outcomes of device implantation to give them realistic expectations such as implantation may result in penile shortening, curvature, scarring, reduced concealability, or damage or destruction of any latent erectile capability.

[Slide.]

Also, we believe that the patient labeling should include a statement that these devices are subject to wear and should not be considered lifetime implants consistent with the physician labeling, a brief description of the available alternative therapies for erectile dysfunction, and instructions on how to care for and use the device during and after the post-operative healing period to reduce the possibility of adverse events such as infection,

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erosion, or mechanical malfunction.

[Slide.]

What I have discussed is our proposed version of FDA's penile rigidity implant guidance document. Although the Agency's consideration of the reclassification of these devices is ongoing, we hope that this guidance document contains those necessary special controls for minimizing device risks.

We invite comments regarding this document which can be sent to the Urology and Lithotripsy Devices Branch at the address listed here. We request that comments be submitted by March 15, 1997. Any comments received after this deadline will still be considered by FDA but held until future revisions of the guidance document.

Furthermore, we will soon be sending this draft guidance document to all manufacturers of penile rigidity implants for their comments.

I thank you for your attention and I will be happy to try to answer any questions that you may have regarding my presentation.

If there are no questions, I would like to

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introduce the next presenter, Linda Dart, who will help provide an update on the PMAs for the Liposorber LA-15 and (H.E.L.P.) systems.

Update on PMAs: Liposorber LA-15 System, Lipoprotein Precipitation (H.E.L.P.) System

MS. DART: Good morning. I would like to update you on the PMAs for the two extracorporeal device systems we have had for removing LDL-cholesterol.

At the Gastroenterology Panel meeting held on April 21, 1995, a recommendation of approval with conditions was made for both Kaneka America's Liposorber LA-15 System and B. Braun Medical's Help System. We are pleased to announce that final approval for marketing of the Liposorber LA-15 System was granted on February 21, 1996.

We are continuing to work with Braun to resolve some complicated labeling issues concerning the H.E.L.P. system which need to be resolved before we can issue a final approval for that device.

Are there any questions? If not, I think Don St. Pierre is going to come back and talk about some of their PMA updates.

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Update on PMAs: Prostatron, UroLume, Reliance

MR. ST. PIERRE: Good morning. My name is Donald St. Pierre. I am the Branch Chief of the Urology and Lithotripsy Devices Branch. Now that Linda has presented an update on the panel's activities related to the Gastroenterology and Renal Devices Branch, I would like to present a quick overview of last year's panel activities for which my branch was responsible.

Although only one panel meeting was held last year, three approvals were granted. Two of these approvals resulted from panel meetings held the previous year. The first approval for 1996 was for the Prostatron Microwave Thermal Therapy System for the treatment of symptomatic benign prostatic hyperplasia in men with prostatic lengths of 35 to 50 millimeters. The panel meeting was held on October 20, 1995 and the PMA was approved on May 3, 1996.

The second approval was for the UroLume Endourethral Prosthesis for use in men to relieve the urinary obstructions secondary to recurrent benign bulbar urethral strictures less than 3 centimeters in length located distal to the external sphincter and proximal to the

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bulbar scrotal junction. The panel meeting was held on January 20, 1995 and the PMA was approved on May 6, 1996.

The third approval was for the Reliance Urinary Control Insert and Sizing Device for the management of stress urinary incontinence in adult women. The panel meeting was held on July 25, 1996 and the PMA was approved on August 16, 1996.

Thank you for your attention. I will now turn the meeting back over to Dr. Melman.

Panel Discussion: P920023/S1

DR. MELMAN: We will now proceed with the review and discussion of the American Medical Systems Endoprosthesis which is a premarket application for a sterile, implantable metallic mesh stent intended to relieve prostatic obstruction secondary to benign prostatic hyperplasia, P920023/Supplement 1.

The first speaker is Dr. Lawrence Getlin, Vice President, American Medical Systems. Once again, I would like to remind you, if you are not an employee of the company, to state your financial interest in this product.

Introductory Comments and Introductions

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MR. GETLIN: Good morning.

[Slide.]

My name is Lawrence Getlin. I am the Vice President of Regulatory Medical Affairs and Quality Systems for American Medical Systems. Today, we are pleased to present information on the UroLume Endoprosthesis for patients suffering from prostatic obstruction due to benign prostatic hyperplasia.

[Slide.]

To begin our presentation this morning, Dr. Joseph Oesterling will present a brief overview of the use of the UroLume device. He will then provide an overview of the clinical study design and results.

[Slide.]

Dr. Oesterling is currently Professor and Urologist-in-Chief at the University of Michigan and he is also the Director of the Michigan Prostate Institute. Following Dr. Oesterling's presentation, I will introduce individuals available today to answer questions from the panel.

At this time, it is my pleasure to introduce Dr.

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Joseph Oesterling.

Device Description/Design and Clinical Study Results

DR. OESTERLING: Thank you very much, Mr. Getlin, members of the FDA, members of the FDA Advisory Panel and distinguished guests. First, I would like to comment that I have no financial interest in American Medical Systems other than the fact that I have been compensated for my time and preparation for this meeting and for my time here today.

[Slide.]

Having said that, I would like to begin at this time and give a brief overview with regard to the UroLume Endoprosthesis as well as for it being an effective long-term treatment for the management of symptomatic benign prostatic hyperplasia.

[Slides.]

As you can see here, on the slide here on the right, it is a device that is placed in the prostatic urethra in order to maintain patency of the prostatic urethra from the bladder neck to the verumontanum.

[Slides.]

Following my description of the UroLume

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Endoprosthesis and Deployment Tool, we will then have a brief overview of the results of the clinical trials that have been conducted here in North America.

[Slides.]

With regard to this device, it is also shown here on this slide on the left, and it consists of a woven, multifilament tubular mesh that consists of a non-magnetic inert biocompatable material. The chemical composition of this alloy is shown on this slide on the right. It contains cobalt, chromium, nickel, molybdenum, manganese and very trace amounts of iron.

Therefore, these patients can undergo ultrasounds, CAT scans and MRIs of their pelvis and prostatic area with one of these devices in the prostatic urethra.

[Slide.]

This device is flexible. It is geometrically stable. It is self-expanding and it provides significant outward radial force to hold back the lateral lobes of the prostate gland and maintain patency of the prostatic urethra.

[Slides.]

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It is available in three lengths, a 2 centimeter length, 2.5 centimeters, and a 3 centimeter device is also available. The internal diameter of this device is 42ÊFrench or 14 millimeters, or 1.4 centimeters.

In the photograph on the right, we can see that it has a very large lumen almost equal to the size of one index finger.

[Slides.]

This device comes loaded on a deployment tool from the manufacturer. In the slide on the right, we have a photograph of the deployment tool. This essentially consists of two concentric stainless-steel tubes with the outer diameter being 21 French, very similar to a routine cystoscope. As stated earlier, the stent is located at the distal end.

[Slide.]

Here is a closeup photograph of that device in its compressed form. It functions much like a Chinese finger. When the diameter is small, it will elongate and then, as the diameter increases, the device will shorten.

[Slides.]

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Here is a proximal end view of the deployment tool where we see a lumen in the center of the device through which a standard urologic telescope can be placed that allows the device to be placed in the prostatic urethra under direct vision.

There is also an irrigation port here that allows for fluid to flow through the device at the time of deployment, again allowing for more precise visualization and proper placement in the prostatic urethra.

[Slides.]

Here is a side view of the proximal end of the deployment tool and we see the finger-grip system. If one depresses this safety latch right here and brings the two finger grips together, this moves the outer sheath toward the proximal end of the device while the inner tube remains stationary. As this occurs, the stent becomes exposed at the distal end of the deployment tool.

This situation is shown in these two slides. The safety latch here has been depressed and the two finger grips have been brought together. This exposes the stent at the distal end of the deployment tool. As it becomes

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exposed, it will automatically expand as demonstrated.

Now, if one depresses the second safety latch, here, and brings the two finger grips completely together, the stent becomes completely exposed and will release automatically from the distal end of the deployment tool.

[Slides.]

This is shown in these two photographs here.

[Slide.]

So, in conclusion, with regard to the device and the deployment tool, I think it is accurate to say that the device is inert and biocompatable and when utilizing this specially designed deployment tool, one can place this device in the prostatic urethra under direct vision in a safe manner.

[Slides.]

Now, I would like to move on and talk about the North American UroLume study group and the clinical trials that resulted from this endeavor.

The US IDE approval was granted in April of 1990 and the first patient was placed in the clinical trial that same month. A second randomized clinical trial was

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initiated in September of 1991 with the first patient being enrolled in October of that same year.

[Slides.]

With regard to the open-label study, there were 13 participating institutions and with regard to the randomized study, there were eight institutions participating. There were a total of 126 patients in the open-label study and 36 patients in the randomized study with 20 patients receiving the UroLume Endoprosthesis and 16 patients undergoing to gold-standard procedure, TURP.

[Slide.]

The objectives of these investigations were essentially fourfold.

[Slides.]

Number one was to demonstrate that the UroLume Endoprosthesis can be inserted in a correct manner endoscopically in the prostatic urethra without adverse sequelae. Number two was to demonstrate that the UroLume Endoprosthesis can effectively hold open the prostatic urethra that was previously closed due to benign prostatic hyperplasia.

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The third was to demonstrate that the UroLume Endoprosthesis does, indeed, become covered with urothelium and that this epithelialization process can occur without adverse events to the prostatic urethra. Fourth was to demonstrate that anticipated adverse events have an acceptably low incidence and when they do occur can be managed safely without long-term sequelae.

[Slide.]

With regard to the patient population and study design, I would like to make these comments.

[Slides.]

The inclusion criteria were that men 45 years of age or older could be included if they were diagnosed with prostatic obstruction secondary to an enlarged prostate gland requiring medical intervention. The prostatic urethra had to be 2.5Êcentimeters or greater in length. There could be no urinary-tract infection and the patient could not have undergone any previous surgery such as a TURP or a TUIP for benign hyperstatic hyperplasia and the patient could not be receiving any medication for this condition such as Finasteride, terazosin or doxazosin.

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Also, there could be no known evidence of prostate cancer in the prostate gland.

[Slides.]

The patients all underwent a very rigorous evaluation consisting of a serum PSA determination, a urine culture. All patients completed the Madson-Iverson Symptom Questionnaire to develop a score from that questionnaire. Patients underwent a peak urinary flow rate determination. A post-void residual urine volume determination was also obtained.

Patients also underwent a cystoscopy to evaluate the prostatic urethra as well as the bladder. They completed a questionnaire with regard to sexual function and they completed another questionnaire with regard to urethral pain and perineal discomfort.

[Slides.]

The pre-insertion summary of these patients would be as follows. In the slide on the left, we have information relating to those that were not in retention, the open-label study, and over here we have those that were in retention also involved in the open-label investigation.

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There were 95 non-retention patients and 31 retention patients.

The mean age of the non-retention patients was 68 years whereas the mean age of those in retention was 76 years. The mean prostatic length of those non-retention patients was 2.9 centimeters and the mean prostatic length of those in retention also was 2.9 centimeters.

[Slides.]

With regard to urinary-tract infection data and median-lobe involvement, the data on these two slides, 17Êpercent of the non-retention patients had a history of urinary-tract infection whereas 17 percent of the retention patients also had a history of urinary-tract infections. 20 percent of the non-retention patients had some degree of median lobe present and 13 percent of those in urinary retention did.

So, with this information, we have described the patients participating in the open-label investigation.

[Slides.]

With regard to inserting this device in the prostatic urethra, I would like to make the following

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comments. Number one, using the deployment tool that we have just described, we can place this device in the prostatic urethra under direct vision. Proper placement would not consist of placing the device up to the bladder neck, but this end of the bladder neck should not extend up into the bladder because if the end of this device extends into the bladder, there is the risk that it may not become completely covered with urothelium.

Also, this device should not extend over the verumontanum because covering the verumontanum may result in some discomfort with subsequent ejaculation after the device has been placed in the prostatic urethra.

Again, using the device, as has been demonstrated here, the stent can be placed in the prostatic urethra under direct vision in a precise way.

Over here, on the slide on the right, we have a radiograph of this device in the prostatic urethra after it has been placed demonstrating that it lies beneath the pubic synthesis in the midline.

[Slides.]

Also with regard to placement of the device in the

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prostatic urethra, it can be placed with a variety of different anesthetics, all the way from general anesthesia to xylocaine jelly only. It is really with regard to this investigation, it was up to the investigator as to which anesthetic he preferred.

But, clearly, this device can be placed in the prostatic urethra without the need for regional anesthesia or general anesthesia. Xylocaine jelly alone can be used and/or oral sedation or IV sedation and, perhaps, a prosthetic block as well.

[Slides.]

With regard to the use of a suprapubic tube, this tube is indicated in some patients. If we look at the non-retention patients, we see more than half of them did not require a suprapubic tube after placement but approximately 48 percent did. For those who did require a suprapubic tube after placement of the device, most of the suprapubic tubes could be removed within several days after the procedure.

The reason for using a suprapubic tube is so that one does not have to place a Foley catheter or another type

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of urethral catheter through the stented area and risk the possibility of dislodgement or migration of the device.

We see similar data over here with regard to our retention patients where many patients did not require a suprapubic tube but, on the other hand, many patients did.

[Slides.]

With regard to results, we followed our patients in meticulous ways starting at one month after placement of the device, then at three months, six months and one year. Then we have long-term data on some patients going all the way out to four years.

But, during this four-year period, patients did come back on an annual basis after one year's time.

[Slide.]

With regard to efficacy, I would like to start first with our total symptom score data.

[Slides.]

Again, here, in these two slides, we have data that relates to the non-retention patients. In the slide on the left, we have the data that goes out to 12Êmonths. Then, in the slide on the right, we have the data that goes

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out to four years.

The magenta color refers to the pre-insertion data for those patients available for follow up at each of the time intervals, and the blue bar refers to the data at the time of follow up whether it is one month, three months, six months, 12Êmonths, two years, three years or four years.

I think what we can see for each period of follow up is that there has been a significant decrease in the total symptom score. On average, it appears that the decrease has been about eight points and this decrease is statistically significant with the p value being less than 0.001 for all follow-up time periods.

I also want to mention that these are matched data such that where we have 97 patients available for follow up at three months, we are comparing the follow-up data here with the data on those same patients prior to insertion of the device.

[Slide.]

Here are the data with regard to the retention patients and, again, we have no pre-insertion data available with regard to total symptom score as these men were in

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urinary retention. Afterwards, we end up with total symptom scores very similar to what we had for the non-retention group in the range of 6 to 7, and it appears to be stable starting already and one month and maintained out to three years of follow up.

[Slides.]

We have broken our total symptom score down into obstructive scores and irritative scores. On these two slides, we have the data from the obstruction information as it relates to the non-retention patients.

Again, we see that there has been a significant decrease in the obstructive symptom score starting already at one month and being maintained all the way out to four years follow up for those patients who are available for evaluation at that time. This decrease--and, again, it applies to matched data here--is statistically significant with a p value being less than 0.001.

[Slides.]

Here are the obstructive symptom score data with regard to our retention patients. Again, we see a decrease pretty much as to what we had observed for the non-retention

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patients. It appears that the decrease in symptom score is observed already at one month follow up and then is maintained over long-term follow up.

[Slides.]

Here are the data with regard to the irritative symptom score. We do see somewhat of a decrease in the irritative symptom score noted already at one month and then maintained over long-term follow up. But the decrease is clearly not what was observed with the obstructive symptom score.

For my own mind, as a practicing urologist, patients who have a lot of irritative warning symptoms making up their symptom complex, I would think, would not be an ideal candidate for this device simply because there is not major improvement in the irritative symptom score when it is broken out and separated from the obstructive component of the total score.

[Slides.]

When we look at our irritative symptom score data with regard to our retention patients, again, we see similar information as to what we had from our non-retention

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patients. There has been a decrease down to around two to three points on the symptom scale and it is maintained over long-term follow up.

[Slides.]

Now, I would like to move on and discuss our data with regard to the peak urinary flow rate information. These two slides, again, relate to the non-retention patients that participated in both the randomized and the open-label studies. Again, the data are matched.

What we can see already at one month follow up is that there is a statistically significant increase in the peak flow rate on the range of about 4 to 5 to 6 mls per second and that increase appears to be maintained all the way up to four years for those patients available for follow-up evaluation.

This increase is statistically significant with a pÊvalue of less than 0.001 value.

[Slides.]

Here are the data with regard to the retention patients participating in the open-label study. Again, we see an improvement in the peak flow rate to a range of 11 to

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14 mls per second, very similar to what we had observed with the non-retention patients.

Again, remember that these patients were in complete retention prior to this device being placed in their prostatic urethra and then, starting at one month follow up, they have been able to achieve peak urinary flow rates ranging from 11 to 14Êmls per second.

[Slides.]

Here are the data with regard to the post-void residual urine volume, again starting out with the non-retention patients. We, again, see that there has been a statistically significant decrease in the post-void residual urine volume with placement of this device in the prostatic urethra, and this decrease has been maintained over long-term follow up.

The decrease, as observed, is statistically significant.

[Slides.]

Here are the data with regard to our retention patients. Again, we see a decrease down into the range of around 40 to 60 mls and it is maintained over long-term

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follow up for those patients available for return.

[Slide.]

Now I would like to discuss the safety issues related to this device being placed in the prostatic urethra.

[Slides.]

I will begin first with our prosthesis tissue coverage. This device is place in the prostatic urethra and then it is over the next several months that urothelium grows through the interstices of the device and eventually, by six to 12 months, the device becomes covered with the urothelium.

What we can see is that, at three months after placement of the device, 67 percent of the patients had 90 to 100Êpercent coverage of the stent. This increases to 87Êpercent at six months follow up and to 90 percent at 12 months follow up.

If we go all the way out to four years, you see about 94 percent have 90 percent coverage or greater. It is not 100Êpercent and the reason for that is that, early on in the open-label study, we were placing the device into the

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bladder neck. In some of those patients, the device did not get completely covered with urothelium.

Based on that early experience, then later on in the open-label study and in the randomized study, the device was placed just to the bladder neck rather than inside it. Similar results were achieved and a greater degree of epithelialization occurred at the bladder neck in those subsequently implanted patients.

[Slide.]

Here is a view on the left of a stent that has been in a patient for two years. You can see how the urothelium has grown through the interstices of the device. Here is the verumontanum and up here is the bladder neck. We have a nice opening maintained through the prostatic urethra over the length of the stent.

Here is a radiograph also demonstrating the stent in the prostatic urethra. You can see that nice patency is maintained and this area right here denotes the external urinary sphincter. So, indeed, for properly positioned patients, urothelium will grow through the device. Complete covering can occur and patency of the prostatic urethra can

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be maintained over long term.

[Slide.]

Now we come to the issue of tissue response. Here we are looking at this pseudopolyploid tissue response to the device in the prostatic urethra. Basically, what this is is the normal response of the prostatic urethra to this device located inside it. There is no evidence of atypia in the tissue that responds to this device in the prostatic urethra.

The normal architectural pattern of the epithelium is maintained and, as best as we can tell, it is a purely benign response to this device in the prostatic urethra. When you look across all time periods of follow up--three months, six months, 12 months, two years, three years and four years--we see that the majority of patients either have no or only mild tissue response to this device in the prostatic urethra.

I think you can see from the previous slide that I showed you what would be considered a mild response. It seems that the greatest response, though, is appreciated at six months to 12 months after placement of the device in the

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prostatic urethra.

[Slides.]

Here we have a gross photograph of a device in the prostatic urethra and then a photomicrograph of a histology slide as well on the right. This would be viewed as a mild response of the prostatic urothelium to this device in the urethra. You can see a little bit of the edematous polyploid reaction shown here.

Then if you look at it under the microscope, here you can see where the wires of the device were and the tissue that has grown between them to cover these wires. You see no atypia under the microscope. We see a normal architectural pattern to the urothelium and there is no evidence here that this is a degenerative process or a dedifferentiation process that could later on lead to a malignant situation.

[Slides.]

These two slides look at the issue of positive urine cultures. we have the data prior to placement of the device and then we have the data when the patients return for follow up ranging from one month all the way out to four

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years. What we can see is that there has been no change in the incidence of positive urine cultures after placement of this device in the prostatic urethra.

[Slides.]

In these two slides, we are looking at the issues of acute urinary retention and hematuria after placement of the device in the prostatic urethra. At one month, 9 percent of the patients had urinary retention and 10 percent had some degree of hematuria. Afterwards, this became negligible over the extent of follow up going all the way out to four years.

[Slides.]

These two slides look at the issues of migration and encrustation. What we can see when we look at the data is that migration for a properly placed stent in the prostatic urethra is minimal and does not occur frequently. It is a rare phenomenon.

With regard to encrustations, we see microscopic encrustations occurring in 11 percent of the patients at 12 months, 14 percent at three years and 29 percent at four years. Again, this phenomenon relates primarily to the

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early patients in the open-label study where the device was placed inside the bladder neck and ends of the device did not become completely covered with urothelium.

With subsequent placement of the device just to the bladder neck rather than inside it, this no longer was an issue.

[Slides.]

Here we are looking at the issue of incontinence. In the slide on the left, we have the baseline data for our patients prior to placement of this device in the prostatic urethra. We broke the incontinence situation down into four major categories; post-void dribbling, urge incontinence, stress incontinence and non-resistance, or total incontinence.

What we can see, if we look at the patients at four-year follow up, there is really no difference between those patients and the data at pre-insertion indication that this device does not cause any untoward effect with regard to urinary incontinence.

[Slides.]

Here are the data with regard to urgency. We

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rated the information according to if you had no urgency, mild urgency, moderate or severe. Again, here is the information prior to placement of the device and then at long-term follow up. Again, what we can see here is that there has been no significant change after placement of the device.

Here we have about 55 percent of the patients reporting none to mild urgency prior to the device and we have similar data here at two years, three years and four-year follow up. It would appear that this device does not cause any more urgency than was already present prior to its placement in the prostatic urethra.

[Slides.]

This slide looks at the issue of urethral perineal discomfort. About 20 percent of the patients reported some discomfort prior to placement of the device in the prostatic urethra. It went up a bit at one-month follow up and at three-month follow up, and this is most likely to due to this foreign body in the urethra. But by six-months follow up, we were back to baseline and then this was maintained over long-term follow up.

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[Slides.]

With regard to sexual function, as data was obtained from the questionnaire that was given the patient, we looked first at erection type as to whether patients were getting a full complete and full erection in their opinion, a partial erection or no erections at all.

Here in the first column, we have the data prior to placement of the stent in the prostatic urethra and then we have the follow up all the way out to four years. Again, I think what we can clearly see from looking at these two slides is that this device has no effect on erections in individuals who are getting full erections or partial erections prior to placement in the prostatic urethra.

[Slides.]

We also looked at the issue of pain with erection. Prior to placement of the stent, 91 percent of the patients had no pain whatsoever and it would appear that we have similar numbers here on long-term follow up as well. At two years, 93Êpercent had no pain, 93 percent, also at three years follow up, and 96 percent at four years follow up with 23 patients available for evaluation.

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So, again, I do not think this device has any effect with regard to discomfort with erection.

[Slides.]

Lastly, we looked at the issue of ejaculation. 89Êpercent of the patients, where data were available, said that they ejaculated prior to the stent being placed in the prostatic urethra. If we then look at three, six, and one-year follow up, there was a slight decline but, in general, not a major decline. If we look at our long-term follow up, again more than 80 percent of the patients reported ejaculation.

Some of these patients did report retrograde ejaculation due to this device being placed in the urethra and some of the semen would go back into the bladder rather than coming out the urethra. But, in general, most patients still reported antegrade ejaculation after this device was placed in the prostatic urethra.

[Slides.]

With regard to removal of the device, 23 devices have been removed for an explantation rate of 16 percent. As shown in these two slides, there are a variety of reasons

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as to why stents were removed. Five stents were removed because of migration issues. Five stents were removed because of persistent irritative symptoms. Four stents were removed because of the ingrowth of the urothelium inside the prosthesis.

Four stents were removed because of incrustation at the bladder neck. Two stents were removed because the prostate had elongated and there was significant growth beyond the stent, either proximally or distally. One stent was removed because of improper placement, one because of incontinence and one because of prostate cancer.

Not all of these removals, you would say, are directly related to the stent such as, for instance, the prostate-cancer patient. But, nevertheless, we reported them as reasons why the device was removed.

[Slide.]

This device can be removed urethraly, endoscopically, without the need for an open procedure. Here is a photograph of a stent that was removed endoscopically in one of these patients. What one simply does is you go up the urethra with a resectoscope, and you

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resect off the overlying urothelium that has grown through the interstices of the device, get down to the stent.

Then you grasp the stent with a grasping force of about a half a centimeter in from the distal edge and rock it back and forth and free it up from the bed that it has been sitting in for six months or a year or so. Then, as you pull in it, it functions like a Chinese finger. It will decrease in diameter and elongate.

Then you can pull the device out to the sheath of the resectoscope without injuring the external sphincter or the urethra and the device can come out intact as shown in this slide.

[Slides.]

With regard to deaths of the patients participating in our randomized and open-label studies, 27 deaths have occurred for a death rate of 19 percent. As you can see in these two slides, there are a variety of reasons why these individuals have died. I would say that there are no absolutely direct stent-related deaths in this group.

A whole variety of reasons exist and they are shown here on these two slides.

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[Slides.]

With regard to success, how well does this device do for relieving obstruction due to an enlarging prostate gland?

[Slides.]

There are a variety of ways to make a success. There is no absolute one way that one must look at this issue. We have looked at it in a variety of ways. The slide on the left looks at the issue of total symptom score. The slide on the right looks at the issue of peak urinary flow rate.

We are presenting here one-year data in the magenta color and two-year data in the blue color. We look at it in three different ways, patients getting at least a 25 percent improvement, patients getting at least a 50 percent improvement and patients getting at least a 75 percent improvement.

In summary here of the symptom-score data, we could say that greater than 50 percent of the patients get at least a 50Êpercent improvement both at one-year follow up and at two-year follow up.

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If we look at the peak urinary flow rate data in the same way, patients getting at least a 25 percent improvement, at least a 50 percent improvement and at least a 75 percent improvement, we see similar success rates. 43 to 45 percent of patients reported having at least a 50 percent improvement in their peak urinary flow rate at one and two-year follow up.

[Slides.]

We also looked at the data as compared to TURP from a randomized study. The numbers are not large but we are in the double digits at 14 for the UroLume group and 13 for the TURP group. Again, if we compare UroLume in magenta to TURP in blue, and look at the number of patients getting at least a 50 percent improvement, the data are quite similar and the p value is not statistically significantly different.

If we look at it with regard to the peak urinary flow rate data, we again see a similar situation where 57 percent of the patients report at least a 50 percent improvement with the UroLume Endoprosthesis and 85 percent of the patients having at least a 50 percent improvement who

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have undergone TURP.

The difference here, also, was not statistically significant although there is a trend with regard to peak urinary flow rate where the TURP patients do slightly better than the UroLume Endoprosthesis patients.

[Slides.]

We also compared our data to the first medication that received approval for the treatment of PBH in the United States, Finasteride. We took the Finasteride data from an article that appeared in the September, 1996, issue of Urology where there was a metaanalysis involving over 1300 patients. We compared the Finasteride data with the UroLume data and we looked at the situation at one-year follow up.

We see that the improvement in total symptom score on average is about eight points with the UroLume Endoprosthesis as compared with 2.3 points for Finasteride. We also compared the UroLume with the Finasteride data with regard to the peak urinary flow rate and we see that the mean improvement with the UroLume Endoprosthesis was 4.7 mls per second whereas with Finasteride or Proscar, the mean

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improvement was 1.4 mls per second suggesting that the UroLume Endoprosthesis results in a significantly greater improvement in both total symptom score and peak flow rate as compared to what would be observed with Finasteride or Proscar.

[Slides.]

So, in conclusion, with regard to our North American clinical trials involving an open-label study and a randomized study where the UroLume Endoprosthesis was compared to TURP, I think it is fair to say that the placement of this device within the prostatic urethra is an uncomplicated procedure with minimal difficulties.

It would appear that the UroLume Endoprosthesis is effective in relieving obstructive symptoms for men who have benign enlargement known as benign prostatic hyperplasia. The urethral urothelium does cover the prosthesis completely when the stent is in contact with the prostatic tissue and this process can occur without adverse events to the prostate gland.

Also based on our data and the experience in these two studies, the UroLume Endoprosthesis can be removed

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endoscopically in a safe and effective manner without additional complications.

[Slide.]

In summary, I would say that the UroLume Endoprosthesis is an effective long-term treatment that is also safe for the treatment of obstructive benign hyperplasia.

Thank you very much for your time.

Introduction of Personnel

MR. GETLIN: Thank you, Dr. Oesterling.

[Slide.]

At this time, I would like to introduce individuals in addition to Dr. Oesterling available to answer questions from the panel. Dr. Howard Epstein is here. He is Chief of the Department of Urology, Associate Professor of Urology, Department of Surgery, University of Florida, Health Science Center.

Also here is Dr. Alfred Defalco, Head, Department of Urology, Chief, Division of Minimally Invasive Surgery and Urology at Harborview Medical Center, Professor or Urology, University of Washington.

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[Slides.]

Individuals available from American Medical Systems are Diane Burnside, Senior Clinical Research Associate, Marta Cody, Biostatistician, and Lisa Pritchard, Senior Regulatory Affairs Specialist.

DR. MELMAN: You don't have any other presentations; is that correct?

MR. GETLIN: Correct.

DR. MELMAN: I would like to throw open to the panel any questions that they may have of American Medical Systems. So, before Dr. DiLoreto says we are fading out, maybe I will ask him--can you hear me?

DR. DiLORETO: I can hear you fine, Arnold.

DR. MELMAN: Do you have a question that you would like to ask?

DR. DiLORETO: I have some questions or some issues I would like to just first clarify. I am the really only working urologist.

DR. MELMAN: I don't understand that but we will talk about it another time.

DR. DiLORETO: I would like to send my regards to

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all there, especially Dr. Sadler.

The questions I had are really more related to probably what is going to end up occurring in the labeling venue. But I had some questions and I wondered what the company's response would be. A lot of it would be very similar to when we talked about the stricture stent.

One is the long-term issues of patients that are going to be implanted. Obviously, there is a wide spectrum of ages of BPH, some men, obviously, in their late 40s, some not until their 90s, but in the younger men, what the potential is going to be or how the company is going to be following these patients that are going to be implanted possibly ten, 15, even 20 years.

I am a little bit concerned about, again, the encrustation issue, the failure rate. Obviously, that may have something to do with the technique and the direction that occurred as far as how the unit was used initially.

I know there were a lot of changes, I think 23, to be accurate, of the modifications in the protocol that occurred during the course of the study. I am still concerned significantly about the hyperplastic responses,

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the issues of long-term, the issues of when and where not to include the irritative symptom group and how to exclude those when you are looking at putting these things in, patients with transitional-cell carcinoma known, whether that group should be excluded.

I would just like some responses to those general questions.

DR. MELMAN: Would you like to respond? This phase is really supposed to be about clarification of the--

DR. DiLORETO: I can hold those until later but those are, basically, my questions. I was able to pretty much hear everything that was going on in Dr. Oesterling's presentation.

DR. MELMAN: Why don't you respond now.

DR. DEFALCO: We are going to set up a carousel of slides here, Dr. DiLoreto. I will address the issue of hyperplasia.

[Slide.]

There are a couple of issues of language I think we need to address. It started out that when folks are looking through the endoscope and evaluating their patients

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in follow up, they saw this tissue inside the lumen of the urethra and called it hyperplasia. Actually, hyperplasia is a histologic diagnosis not an endoscopic one so we were faced with a dilemma sort of right off the bat.

What I would like to do is bore you for a moment and go through some of the aspects of true hyperplasia histologically and then address the issue, as we saw it, of the endoscopic event.

This is normal urothelium. It is a very specialized tissue, as you know. Usually, the number of cell layers are five to seven but they can be up to ten or 12. The architecture is very precise. There is a layer of epithelium, a sub-epithelial layer and, of course, a layer of lamina propria which contains fibrous tissue and, obviously, blood vessels.

[Slide.]

There are varying degrees of hyperplasia. There is some evidence, at least over the last 20 or 30 years, that hyperplasia of urothelium is actually a continuous process rather than each classification or some classification being a de novo event.

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It appears as though the first stage of true epithelial hyperplasia is just a thickening or a hyperplastic response of the urothelium, the epithelial layer or the transitional-cell layer, so that it becomes more thick. The number of cells graduating out from the basement membrane increases in size and in number so there may be up to 15 to 25 cell-thick responses to a number and to a variety of stimulations.

Obviously, infection is one, but there are a number of events which occur which are benign in character in which the epithelium or urothelium, I should say more properly, becomes thickened. This is an example of benign hyperplasia response with no antecedent event in a patient--this is in the prostatic urethra--with no evidence of previous infection.

DR. DiLORETO: I'm sorry; could you speak up just a little bit. I am missing a few bits of this.

DR. DEFALCO: The first slide demonstrates the thickening of the urothelium in a patient with no antecedent events such as infection or trauma. This patient had a TUR and had chronic benign prostatic hyperplasia. Again, there

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is no atypia. The architecture is relatively maintained in this patient except for the thickening of the urothelium.

[Slide.]

The next slide is possibly the next event or next stage in true hyperplasia of the urothelium with the formation of buds or nests of epithelial cells, again of minimal or no atypia. These are Von Brun's nests snuggled underneath the layer of urothelium.

DR. MELMAN: You are talking about bladder here, not prostate.

DR. DEFALCO: This is actually anywhere in the urothelium, anywhere from the renal pelvis to the bladder and in the urethra. All of these have been reported.

[Slide.]

The next slide, again, shows a patient with cystic changes. Again, these can occur--this particular one is actually taken from the bladder neck. It shows cystic changes probably emanating or evolving from Von Brun's nests.

[Slide.]

The next one is a patient--again, this is taken

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from the bladder neck of cystitis, urethritis glandularis. The first reported case of this actually in the urethra was in 1974, so it does occur throughout the urinary tract and it can also occur in the renal pelvis.

I think, in conclusion, we can say that true hyperplastic response has a series of steps. The urothelium, again, can present in a variety of forms. There seems to be some stepwise progression from simple hyperplasia, epithelial thickening to the formation of colonization, actually, of the epithelium.

There are a number of studies which have failed to show any significant evidence for progression to malignancy with hyperplasia. Often, one can see these changes in patients who have carcinoma, but there really is no evidence that they progress to a malignant state.

[Slide.]

This is a slide of one of the patients who approximately six to eight months after having a stent placed has the designation, "hyperplastic response," but this is an endoscopic finding. What we see here is the pseudopolyploid villus changes in the urothelium.

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[Slide.]

Again, a more close-up photograph of that same area where we see this opalescent, edematous reaction in the urothelium with some hemorrhage in the basal portion of the pseudopolyploid projection of urothelium.

[Slide.]

However, when we look at this under the microscope, we see something which is very, very dissimilar to what we have been talking about with regard to hyperplasia, and that is we see a very orderly construction of the pseudopolyploid area or projection with orderly epithelium. There is no atypia. There is preservation of architecture.

Again, we see an edematous lamina propria with some hypervascularization.

[Slide.]

Again, this is a very similar--again, taken from the same patient. This is actually TUR tissue. This patient had the stent removed because of irritative symptoms. This is TUR tissue which essentially shows the same type of response.

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[Slide.]

This is a patient who had a stent in for two years, a little over two years. As you can see, we are just in front of the verumontanum here. There are stent wires which are projecting from the prostate. This prostate grew at an alarming rate over a period of time and obstructed this patient proximal and distal to the stent primarily. But, again, you can see the wires are exposed in the prostatic urethra. There is no evidence for encrustation here.

There are small areas of the so-called pseudopolyploid reaction throughout this patient's prostatic urethra.

[Slide.]

Again, what we see here is a compressed lumen with the wires in place, all covered, and a very orderly architecture of edematous urothelium over the wires adjacent to the lumen.

[Slide.]

This is just a more high-power view of the same thing, again with preservation of architecture and no atypia

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and, again, a situation which is a urothelial response which is not hyperplastic in nature if one is using the common histologic diagnosis of hyperplasia.

[Slide.]

We have some animal studies. Again, this is a sheep urethra after placement of the stent for about three months. As you can see, there is, again, preservation of architecture, normal epithelium. We do see, I think quite interestingly, that the wires have now become fully covered with urothelium at the present time and actually are in contact with the urethral lumen.

[Slide.]

This is just a high-power view of the same animal at three months. Again, you can see the similarities between this experimental animal and the human. They are almost identical.

[Slide.]

At one month, again, you see a much more orderly progression and regression, if you will, of the polyploid response. The wires are now covered and, again, there is preservation of the architecture of the epithelium and no

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evidence for atypia at one year in this experimental animal.

Thank you.

DR. MELMAN: Could you answer the question in terms of the labeling whether this should be used in people who, for example, have carcinoma in situ of the bladder, or polyploid tumors of the bladder, because then there would be this free egress of urine anyhow into the prostatic urethra. But you would be holding the prostatic urethra open.

So is that a contraindication to the use of this device?

DR. DEFALCO: Again, it would be difficult to answer that question with the evidence that we have at the present time. However, I think that if there is carcinoma in situ of the bladder, you are at risk at any point in time in developing a carcinoma extension to the prostatic urethra.

I am not sure that the stent, per se, because it is covered, would be an additional risk fact. You wouldn't be putting the patient, I don't think, in more harm's way in that situation.

DR. MELMAN: But you didn't have any patients in

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that category.

DR. DEFALCO: No; we did not.

DR. DiLORETO: I would just like to regress back a bit to the hyperplasia issue. I am not aware of any long, long-term studies. Basically what we are talking about doing is generation of potential long, long-term studies of what happens in these changes given 20 years worth of implantation and irritation.

I heard, and it was sort of fading in and out, some issues concerning--I believe what was mentioned was cystitis glandularis and, at least from my standpoint, and I am sure from the urologists' standpoint, potential changes that can occur with that.

I still am a bit concerned about the issue of, again, short-term which could be five years or less is a lot different than 10, 15, 20 years of irritation from having one of these things in. I am concerned about that. I just wondered if anybody else on the panel feels that way or the company can respond to how that is going to be looked at and what the ramifications of this are.

DR. MELMAN: We are going to hold that until a

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little bit later on.

DR. DiLORETO: Okay.

DR. MELMAN: Let me ask if there are any other questions.

DR. BENNETT: The same concerns that Bob had as far as labeling and how long.

DR. JONES: I really think, from what I read concerning the UroLume prosthesis, it did very good. There were some complications but not too many. I never use them. Of course, I never use them. I always treated with Hytrin, my patients, before I stopped practice.

DR. MELMAN: Do you have any question that you would like clarified?

DR. JONES: No.

MR. GATLING: No.

DR. HUNTER: What is the actual force applied by the stent to the wall of the prostate. Would you answer that? What is the actual pounds per square inch or whatever force, vis-a-vis--the opposite corollary of that would be how much would it take to bend it or crush it. I don't remember that.

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MS. PRITCHARD: I am Lisa Pritchard with American Medical Systems. We actually can't answer that question because the force is dependent upon what its constrained diameter is within the prostate.

DR. DiLORETO: Mary Jo, I am not getting everything here.

DR. HUNTER: In other words, the more you compress it, the more pressure it takes to compress it.

MS. PRITCHARD: I can show you the testing data that we have that showed--

DR. HUNTER: The reason I ask is on some of the photomicrographs that were displayed, there were some tubular structures compressed. Do we know what those were? Were those blood vessels? Were those ducts, BPH tissue, or all of the above?

DR. DEFALCO: These are beautiful photomicrographs.

DR. HUNTER: Wonderful. I'm sorry Robert can't see them.

DR. DEFALCO: They are very, very exciting. The structures that you see, the round, clear areas, are

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actually the areas of the stent wires themselves. Those are unassociated with infection and disturbance of any architecture at all. We don't see compression of vessels. We see minimal compression of the muscularis as well in the deeper layers so there is probably very little compression of any tubular or ductular structures.

DR. HUNTER: Was there any attempt to measure ejaculation volume because all we know is that some patients reported retrograde ejaculation. But that could have been compression of the prostatic duct so that there was no fluid. Was there any attempt to measure that? Do we have any of that information?

DR. DiLORETO: Mary Jo, I am missing part of this.

DR. DEFALCO: We do not have that information.

DR. HUNTER: My question was was there any attempt to measure the ejaculation volume changes because the patients that describe retrograde ejaculation might have had less volume and not really been retrograde ejaculation. And does the stent keep the bladder neck open?

DR. DEFALCO: The stent does keep the bladder neck open probably by virtue of the mechanism of contiguous

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radial force. But when we look at these folks, we do not see a large fusiform configuration. As I think Dr. Oesterling showed you, there is a patent lumen all the way to and including the bladder neck including those patients who have had their stents placed proximal to the bladder neck.

DR. HUNTER: So the bladder neck is maintained open.

DR. DEFALCO: It is maintained open.

DR. HUNTER: The urinary-retention group did not seem to do quite as well in terms of their flow rates and volumes. Was that because the prostate was larger or the prostate configuration--it didn't appear that it was. Was there a difference in configuration of the prostate or do you think that the bladders were not as compliant or oversized?

DR. DEFALCO: I think that is correct. My impression and sensation is that the patients had a similar configuration, anatomic configuration, of their prostate but they were older gentlemen and they had more chronic obstruction. I think they probably had some decompensation

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of bladder detrusor function.

DR. HUNTER: Would you personally recommend urodynamics in patients before using this device?

DR. DEFALCO: I personally would not. There are two reasons. One, I think, is that we know that urodynamics do not always predict how a bladder is going to do after decompression. Also, there is a wide variety of patterns in the patients that we have examined who have prostatic hyperplasia and chronic obstruction.

DR. JETER: I just had a concern about the lack of follow up on these patients. As I look at it, as I read it, the two-year follow up, eight patients in each group have missed their follow-up visits which would be 50 percent of the TURP patients and 40 percent of the UroLume patients.

I can understand, perhaps, how they might not be able to get there but I would think that there would have to be a way to get to these patients to get the information for follow up.

MS. BURNSIDE: Diane Burnside from American Medical Systems. When we first originally started these studies, the follow up was only for one year. That is what

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was agreed upon. And then, as we were going along with the study, the FDA did request that we extend that out annually until we got PMA approval.

So we went back to all of our institutions. They went to their IRBs and we asked for additional follow ups annually at that time. Then they had to go out to their patients and request that they come back in for follow up. Those patients had all signed informed consents that asked them to come back just through one year.

So the patients didn't feel obligated to come back to us and we did the best we could, and so did the doctors, to try to get them to come back in. But they only signed up for the study for one year. So we were able to get some of them to come back in but we were unable to get all of them to return for follow up after the one-year visit.

DR. SADLER: I have a few questions that I would like to ask. One is the implication has been that this is essentially a permanent implantation of a foreign body in the urethra to dilate it. Yet, 73 percent of the subjects exhibited hyperplasia through the interstices in this thing.

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It strikes me that it is not illogical to presume that they would eventually grow enough tissue through these openings to close the urethra down again.

At four years, you don't have evidence that this is significantly happening, but there is significant hyperplasia there and it seems to me that an organ that is hyperplastic and with the stimulation of a foreign body, we are likely to see more overgrowth and, ultimately, some occlusion.

I would like your thoughts on that.

DR. OESTERLING: When you look at these patients all the way out to four years, the maximum response is usually observed at six to 12 months. Then, after that, the response calms down. It settles down and then when you follow these patients out to three and four years--

DR. DiLORETO: Can I have Dr. Oesterling speak up, please.

DR. OESTERLING: This is Joseph Oesterling speaking. I am answering the question dealing with whether or not there is a likelihood that these prostatic urethras can reobstruct from this hyperplastic, as we have been

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calling it, overgrowth coming through the interstices of the device.

My feeling about that is that is not likely to happen. The reason that that is not likely to happen is that we see the greatest response at about six months to 12Êmonths after the thing is placed in the prostatic urethra. Then, when we follow these patients out further to two, three, four years, the response calms down and we see no further progression of it.

When we look at our patients, even the 73 that you mention, the response that we have there in most of them is mild and moderate. It is not really severe at all. So, later on, I think the response settles down and we have not seen any evidence that it is going to pick up again and become more severe with more time. But, again, the follow up is out to four years in these patients.

DR. SADLER: I would also like to ask, as I look at this and you contrast it with at TURP, I wonder what is the procedure duration for placing a stent. Does it take ten minutes, an hour, two hours?

DR. OESTERLING: That is a very good point. In

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general, it would take about ten minutes to place a stent in a prostatic urethra. That is substantially shorter than it would take to do a TURP which is, on average, around 30 minutes to 45 minutes.

The other potential advantages of this device is that you don't need an anesthetic whereas a TURP, by and large, we do them under spinals or generals or occasionally prostatic blocks. There is minimal bleeding associated with this device. You can place it, clearly, in debilitated men who would have coagulopathies and so forth.

And the recovery period is non-significant because you haven't done any incising and one has not done any resecting. You simply place the device, the prostatic urethra is open and the patient can go home at the end of the day.

DR. SADLER: I noted that the majority of the trial was carried out in five institutions. Do you have any information on how many operators there were overall who carried out the procedure? I am concerned in that a significant minority were unsuccessful, were removed, were done over. I want to know how difficult this is to get it

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right.

DR. OESTERLING: I will ask Diane Burnside to comment on the exact number of investigators, but I can comment on your latter concern, is it difficult to place the stent in the prostatic urethra. In general, I think the answer is no. There is clearly a learning curve and I think we need to place five to ten of these devices to get experience with it.

But after a urologist has place five to ten of these, I think it can become a very routine procedure. We place it endoscopically with the use of our cystoscope. All of us urologists are comfortable with the cystoscope. We are all comfortable doing endoscopic procedures in the urethra. I think this is just one more of these types of procedures.

But, clearly, I think, one needs to have some experience placing several of these before you just simply say it is a real routine, old-hat kind of thing to do.

DR. SADLER: There was only a very small number of urinary-tract infections after the procedure and I thought that was a very favorable thing. But I would like to know

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if those infections were able to be cleared. Since you have a permanent foreign body in the urinary tract, I was afraid that it might become colonized and that those few patients who did become infected might remain infected.

DR. OESTERLING: The data, as we presented it here, relates to the bacteria in the urine and having a positive culture. These patients were not symptomatic from this infectious process and these infections or positive urine cultures were cleared with appropriate antibiotic therapy. They did not go on to become chronic situations.

DR. SADLER: Okay. Thank you.

DR. OESTERLING: As far as the investigators go, I think we just had that slide up. While there were several participating institutions, at several of the sites, there were a couple of investigators. So I guess, here, at our different sites, we had a total of--

MS. BURNSIDE: We had 18 institutions.

DR. OESTERLING: How many did we have total, Diane? It looks like there were a total of 20 investigators at 13 sites in the open-label study and 8 sites in the randomized study.

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DR. SADLER: That tells me how many investigators. It doesn't tell me how many associates or residents they had who were also carrying out the procedure which is an important question since the success rate was less than 100Êpercent and the investigators are all experienced and highly qualified urologists. I wonder whether it was their finding an unsuccessful procedure or whether it was their resident or their junior associate or just how many times this was carried out and how well it was done.

I am concerned that you have a procedure that, while it appears superficially quite straightforward and uncomplicated, that that may be a problem, that it looks too easy and people without experience may do some real damage. This is a powerful wire that expands strongly and it is a foreign body that lives in the patient.

DR. OESTERLING: From my own experience, when I participated in the study at the Mayo clinic, I placed all of these devices in my own patients. I did not have assistants or residents doing these procedures for me. I did them all.

As to what exactly went on at the other

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institutions, I do not know. Maybe Diane Burnside or Howard Epstein or someone else could comment on that.

DR. EPSTEIN: Good morning. I am Howard Epstein, one of the other investigators. I can say that it is quite straightforward and simple to put in. I think that now, especially since the stent has been out for a stricture application, if anyone knows how to use the applicator, the real judgment comes from where to place it.

That really will take, as Dr. Oesterling said, a few cases to know where you should put it in the prostate, just like where you should put it over a stricture. But it is pretty straightforward.

I have shown, for example, residents how to do it and they have picked it up quite simply. So I think any urologist who has had some practice should be able to do it without much problem.

DR. MELMAN: I have a few questions. One is that, first of all, I think you are mixing apples and oranges, and that is that the hyperplasia that you are talking about is--this is transitional-cell hyperplasia of the mucosa, not benign prostatic hyperplasia. It is two different

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hyperplasias.

So you are really not treating the BPH. You are creating another type of hyperplasia that is a reaction to the stent.

I was a little surprised that half of the people needed SP tubes. That is another procedure. I am just wondering how you decided who needed an SP tube. It is not, necessarily, a benign procedure. You can cause some damage with it. Tell us about that.

DR. OESTERLING: Again, this is Joe Oesterling. I think the reason we were on the safe side--again, many of these SP tubes are placed early on in the studies related to the fact that we were doing the procedure under general anesthesia and under spinals, and we didn't want to place the catheter to the urethra.

So we just put a percutaneous suprapubic tube in as they recovered from their anesthetic or until they demonstrated that they could really void well. So it was more in a prophylactic way than absolute requirement. As we did more and more of these procedures under local anesthesia only, or with sedation, the need for the suprapubic tubes

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declined.

Also I think what can happen is that as you do this procedure, you have your irrigant flowing in. If you are not careful, you can overdistend the bladder and produce a hypotonic bladder for 12 hours or 24 hours and so forth. That can be a reason why the patient may not be able to urinate really well once this stent is placed.

But these suprapubic tubes are placed at the time the stent was put in and then left in for 12 hours, 24 hours, whatever, until the patient was able to urinate in a free and easy way.

DR. MELMAN: So, today, if you were putting one in under local anesthesia, would you put a suprapubic tube in?

DR. OESTERLING: I would not.

DR. MELMAN: A couple more questions. The prostatic urethra extends about 11 millimeters distal to the verumontanum. You are only putting it up to the verumontanum, and you are really not putting the stent into about a third or less of the prostatic urethra. Yet you are saying that the flow rates were pretty much normalized.

I don't understand how that is possible. Maybe

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you could explain that to me.

DR. OESTERLING: I think the whole ability to urinate before and after TURP is not well understood even today, either. My comment with that would be when we routinely do a TURP, or at least I speak for myself--

DR. DiLORETO: Could I ask Joe to speak up a little better, please.

DR. OESTERLING: Yes. When I do a TURP, I do not resect out distal to the verumontanum. So I don't think that I am effectively treating that tissue even with my TURP. I agree 100 percent with you that the veru is still some distance from the apex of the prostate. If one wanted to be complete with regard to treating the whole channel of obstruction, you would want either your TURP, your stent, or whatever you are doing, to go all the way out to the apex.

It probably is not necessary to get all the way out to the apex and, if you do so, we probably would risk some degree of incontinence. So I think, as the data would point out, when we place this device from the bladder neck to the verumontanum, we are able to achieve significant improvement with regard to the ability to urinate even

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though the tissue beyond the verumontanum distally has not been stented.

I am not sure it is necessary to stent it.

DR. MELMAN: If you are comparing TUR data, where you don't cut out the tissue distal to the veru as opposed to comparing it to data where you do a total prostatectomy where you do take the tissue, then you may find much larger differences in flow rate that you are not accounting for.

You didn't do it and so I am not asking you for it, but when I do a TUR, I cut the tissue distal to the verumontanum. I think it is a more complete procedure.

Let me just ask another question. The way you presented the data is not the way we treat patients; that is, we don't recommend a treatment based upon the flow rate. The type of treatment we recommend is usually dependent upon the size of the prostate and where the middle lobe is.

In none of the data that you presented, did you talk about the efficacy of the treatment for a person who might have a 30-gram gland from someone who had a 70-gram prostate. So what I would like you to do, and maybe you have done it, is compare the efficacy dependent on gland

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size, not upon flow rate, because that is really--when you are presented with a patient, how are you going to decide what treatment to recommend to that individual.

DR. OESTERLING: I think that is a good point. Maybe while I am getting a couple of slides together with regard to that issue, let me just make a few comments. One, the only restriction, in terms of size, is that the prostate be greater than 2.5 centimeters--2.5 centimeters or greater.

Let's assume that you have a 5-centimeter long prostatic urethra. You can put multiple stents in if one chose to do that. You can start at the bladder neck, put a stent in, put the second stent inside the first one, put the third stent inside the second one and go all the way out to the verumontanum if the patient chose this form of treatment.

[Slide.]

When I think about this device and how I would use it if it achieves FDA approval, in my own practice, would be to present the prostatic stent as another minimally invasive treatment option that we have available, like we have got laser prostatectomy, we have got TUIP, we have TUNA, we have

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Prostatron--we have a number of these things in conjunction to our three medications--and talk about the pros and cons, work together with the patient and, together as a team, we decide whether or not he is going to choose a stent or not.

So I would probably present the device as an alternative with our other treatments we have available. I think where it is ideally suited is for the debilitated individual who is in urinary retention and he doesn't have the manual dexterity or doesn't want to go through catheterization or you don't want to put him through the TURP.

You can put a stent in in ten minutes and he is on his way home afterwards. And he can urinate well.

As far as breaking the data down, in terms of size of the prostate, I don't think that this slide here really addresses that, how our flow-rate and symptom data compare with 20-gram prostates versus 70-gram prostates or prostates with a 3-centimeter urethra versus a 5-centimeter urethra.

Do we have that information?

MS. CODY: I am Marta Cody from American Medical Systems.

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[Slide.]

This is a slide summarizing the regression we did to see what baseline variables affected our efficacy variables. We looked at total symptom score at one year, obstructive score at one year, irritative score, peak-flow and residual urine volume. And we looked at the effect of age, prostate length, UTI history, prostatic obstruction--

DR. DiLORETO: Mary Jo, I am missing some of this.

DR. MELMAN: Please speak a little louder.

MS. CODY: Median-lobe obstruction, trabeculation of the bladder, prostate size and tool type.

This slide summarizes what variables affected the outcome variables. For prostate size, it was not found to be significant for any of the efficacy variables.

DR. MELMAN: What was the range of gland size of the patient?

MS. CODY: Less than 40 or greater than 40 was used for this analysis.

DR. MELMAN: Could you tell us how many were less than 40, how many were greater than 40?

MS. CODY: We will have to get that from a

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different slide.

[Slide.]

This is the distribution of prostate size among the different groups.

DR. MELMAN: So most of the prostates were less than 40 grams, the overwhelming majority.

MS. CODY: Right.

DR. MELMAN: Are you going to show us the degree of efficacy based on this now?

MS. CODY: Sure.

[Slide.]

First of all, we looked to see which factors affected the efficacy variables and then we stratified by those that were significant. Prostate size was not found to be significant and so we did not do any stratification by prostate size.

DR. JONES: You mentioned middle lobe. That was one of the complications for migration using the stent. Joe, I didn't hear you mention anything about middle lobe. When you cystoscope the patient and find the middle lobe, do you give him other options rather than the stent placement?

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DR. OESTERLING: Dr. Jones, that is a very good point. Based on the experience that we acquired during these two studies, if a person has a significant middle lobe, I do not think he is a good candidate for the stent.

DR. MELMAN: Significant?

DR. OESTERLING: Significant meaning that you see a protrusion up into the bladder neck into the bladder. If you can see that there is a well-defined median lobe present, I do not think he is a candidate for the stent.

DR. MELMAN: 20 percent of the patients had middle lobes.

DR. OESTERLING: Had some degree of middle-lobe. We commented on it. Again, those patients were patients that were involved in the first part of the open-label study. The reason I do not feel that it is appropriate to put a stent in a patient who has a significant median lobe is that we are going to ask the stent to sort of depress that median lobe down and stay out of the way of the bladder neck.

When that is occurring, the top part of the stent, at the 12 o'clock position, will not get covered with

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epithelium and then the device will be at risk for encrustation.

DR. JONES: That's right.

DR. OESTERLING: So I would say that in my own practice, if I have someone who has got a significant median lobe present, I would not place a stent in that individual.

DR. HUNTER: If I look at the data, I think a lot of failures occurred with bladder-neck contractures. In your indications and so forth, you are talking about using this for treatment of bladder-neck contractures. Does this work for bladder-neck contractures in your opinion? I want to hear from all three of the doctors.

DR. OESTERLING: Right now, this device has FDA approval for the treatment of benign recurrent bulbar urethral strictures. We are now considering for the treatment of benign prostatic hyperplasia.

In compassionate use, I have placed this device in several patients with bladder-neck contractures after a radical prostatectomy. In those very few patients that the device has been placed, it has worked quite well. It has been effective in dealing with these very difficult

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bladder-neck contractures that nothing seems to work well for.

But the experience has been in a compassionate use. It has been very limited. That is all I can comment on at this point.

DR. JONES: Joe, do you get incrustation when you put them at the bladder neck because I think it extends a little beyond the bladder neck.

DR. OESTERLING: In this situation that Dr. Hunter brings up of a bladder-neck contracture scenario, again, you have to be precise with your placement. In the three that I was involved with, it just went right inside that bladder-neck contracture area. I did not allow it to extend up into the bladder.

Then, what I felt happened when I scoped these people subsequently is that this pseudopolyploid tissue response exuberated a little bit over the ends of the device right there at that bladder-neck contracted area and the device was covered.

But I would not recommend extending this device into the bladder. I would not.

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DR. EPSTEIN: I would have to echo what Dr. Oesterling said. I have done one under compassionate use and that patient had recurrent bladder-neck contractures from a radical prostatectomy and it has worked out quite well with him. But I think that it does show promise in that application, again, as long as, again, the thing isn't protruding way into the bladder, it is just right at the contracture.

But that is a tough problem and I think that this would be a good solution.

DR. DEFALCO: This is Dr. Defalco, again. Our experience with compassionate use could make a soap opera. We had four patients that came to us with the most dramatic stories of debilitating comorbidity from having had a radical prostatectomy and radiation therapy, had been in and out of the hospital on a weekly, sometimes almost daily, basis with obstruction and bleeding.

We placed the stent, as Dr. Oesterling described, just within the bladder neck and all of these patients, every one of them, have had a dramatic release of obstruction and symptomatology and morbidity.

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DR. MELMAN: Thank you very much.

We will now take a five-minute break, a compassionate break.

[Break.]

DR. MELMAN: We will now have at FDA presentation.

FDA Presentation

Overview of Clinical Studies

MR. SEILER: Good morning. I am Jim Seiler, the lead reviewer for the PMA supplement.

We are here today to discuss a new indication for the UroLume device, a metallic expandable stent originally approved on May 6, 1996 for the indication of bulbar urethral strictures.

[Slide.]

The new indication is for the treatment of benign prostatic hyperplasia, or BPH. Please note that this slide reprints the indicated use as currently seen in the labeling but the sponsor has elected to drop bladder-neck contracture indication from the labeling due to an insufficient number of patients enrolled in the study with this condition.

No device design issues need to be addressed

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because the UroLume is identical to the original device including identical deployment tools. Therefore, the PMA focusses on the clinical study.

The information presented by Dr. Oesterling accurately reflects the data in the PMA supplement so I will focus on some of the issues encountered during review of the PMA supplement.

There were several concerns identified with the study design and the conduct of the study. First, the clinical data consisted of a non-randomized, baseline controlled study and a randomized controlled study. The randomized study was not completed because of low patient enrollment which is attributed to patient unwillingness to receive the TURP surgical treatment when other less invasive treatments were available.

Since no conclusions could be drawn from this incomplete study, the data from the device-treated patients were combined with the non-randomized study to form a larger baseline controlled study.

[Slide.]

The resultant combined database consisted of 146

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patients for safety analyses but only 115 for effectiveness analyses since 31 patients were in urinary retention at device insertion and, therefore, no meaningful baseline flow or symptom data could be obtained from these patients.

Use of the baseline controlled study has its own weaknesses in that the risks of such a study must be assessed without benefit of an active control. This type of study design relies heavily on the physician's own experiences and knowledge of the literature on which to evaluate the clinical results and conduct a risk/benefit analysis.

Another concern with the study involved the uneven distribution of patients at the investigational sites.

[Slide.]

For example, the non-randomized study was conducted at 13 sites, 11 in the U.S. and two in Canada. But 60 percent of patients were enrolled at just four sites. The randomized study was conducted at eight U.S. sites but 75Êpercent of patients were enrolled at just two sites.

Fortunately, the sponsor was able to provide a satisfactory statistical justification to pool the patient

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data and, therefore, this was not an issue.

The conduct of the study also included many deviations from the study protocol regarding patient selection, insertion procedures and patient evaluation. Although these deviations complicated the analyses, it was determined that they did not impact the results and hence these patients could be included in the overall analyses.

[Slide.]

The effectiveness data clearly show improvement in uroflow. As you can see from this graph, pre-insertion peak flow was approximately 9 ccs per second which increased to approximately 14 ccs per second at 12 months.

[Slide.]

This next graph demonstrates the improvement in obstructive symptom score from a score of approximately 10 before the device to a score of approximately 3 after it.

[Slide.]

The results for irritative symptom score were less dramatic than the obstructive symptom score. This should be expected given that the device is a foreign body. Irritative symptoms should be considered when deciding

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whether the stent is the best treatment option for the patient.

I will now discuss some of the risks associated with the device.

[Slide.]

Risks to the patient include hyperplastic tissue response, incontinence, urethral pain, hematuria, encrustations, migration and device insertion and/or removal trauma. Hyperplastic tissue response which represents tissue growth within the stent was 55.7 percent at 12Êmonths, the majority of which was classified as either mild or moderate severity.

Although this level of ingrowth is clearly of concern, only four device removals within two years were attributed to hyperplastic ingrowth. Dr. Herrera, FDA's medical officer, will elaborate more on this matter during his presentation.

Incontinence is another potential risk. The overall data on incontinence as an adverse event indicates 60 percent of patients were incontinent prior to insertion of the device and 45.8 percent were incontinent at 12

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months. Only one device removal was attributed to incontinence.

Symptom data which compares the patient's incontinence pre-insertion and at 12 months provides a clearer picture of this adverse event. These data indicate that 57.5 percent of patients felt the same, 21.8 percent felt better and 20.7 felt that their incontinence was worse at 12 months.

The overall data on pain indicates that while 20Êpercent of the patients experienced urethral pain prior to the device, at one month, this rose to 43 percent but then diminished with increasing follow up and returned to 20Êpercent at 12 months.

Another method to consider with regard to pain data is how the patient felt at 12 months compared to pre-insertion. This type of pain data indicated that 72.2 percent of patients felt the same, 14.4 percent felt better and 13.4 percent felt worse pain at 12 months.

Hematuria, another expected adverse event from the stent, was reported in 17 patients through the 12-month follow up but only one of these patients required treatment.

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22 cases of encrustations on the stent at the bladder neck were reported on the first 70 patients. This decreased only two cases out of the remaining 76 patients after the new modified positioning instructions were implemented, the purpose of which was to prevent any part of the UroLume from protruding into the bladder neck.

Migration after device insertion, an adverse event unique to this method of BPH treatment, occurred in only seven of the 146 patients enrolled of which five required removal.

[Slide.]

Based on 146 patients, 16 percent of patients had their devices removed at insertion mostly attributed to positioning and device-size errors. Of these 23 removals during the insertion procedure, 15 were replaced with another stent and the remaining eight did not receive any device.

Removals after insertion, through all follow up, were 16 percent. This table shows that 15 removals occurred before one year and 10 removals after one year.

[Slide.]

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This next table lists the causes of device removal. Sexual function data were collected. However, these data were added to the protocol after the study was in progress; hence, only approximately 35 percent of patients were available to evaluate for sexual function.

These limited results do not indicate a worsening sexual functioning condition except for the incidence of retrograde ejaculation which increased from 0 percent pre-insertion to 28.1 percent by the by the 12-month follow up.

Although there were deficiencies with the study design and the conduct of the study, the data indicate that the device is effective at increasing uroflow and improving obstructive symptoms. However, there were specific risks associated with this type of device that need to be looked at very carefully when determining the appropriate patient population and conducting the risk/benefit analysis.

Dr. Hector Herrera will now discuss a couple of issues in more detail and present the charges to the panel.

Clinical Issues and Charges to the Panel

DR. HERRERA: Good morning. Due to unforeseen

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circumstances, Dr. Jevtich, the clinical reviewer for the PMA supplement, is unable to be here and I will be filling in for him. My name is Hector Herrera. As is Dr. Jevtich, I am also a urologist within the Urologic Device Branch.

The previous speakers have done an excellent job. I will be brief and only present a couple of issues that I believe warrant further discussions. I will then close up with the charges to the panel.

[Slide.]

The first issue that I would like to discuss is the patient population. For the most part, the recipients of this device were of advanced age. Even though the inclusion criteria start at age 45, only ten patients were under the age of 60.

The mean age for non-retentive patients was 68 years and the mean age for retentive patients was 76 years. The non-retentive patient population was slightly older than we have seen in other BPH studies.

[Slide.]

The following table shows some of the important patient demographics for this study. As you can see, a

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number of patients had a significant medical history. Also considering that 27 patients had died for reasons unrelated to the stent with the primary reason being cardiovascular, lung and renal disease, this is not a younger, healthy group of patients.

[Slide.]

Would like to move to epithelialization of the stent. Epithelialization after the placement of the stent is a natural reactive process of the prostatic urethra. It was interesting to notice that this process was somewhat faster than the ones in the previous PMA study for urethral stricture.

For the stricture study, at six month, 90 to 100Êpercent were covered in 68 percent of the patients. For this study, the percentage increased to 87 percent of the patients. This may be due to the fact that the stent was used for the first time in the lumen of an active gland.

In the stricture study, as in all previous stent applications, the stent was placed in the lumen of a relatively non-reacting body channel like the bile duct, vascular channel or bulbar urethra.

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With this in mind, I would like to move on to tissue ingrowth into the stent. Two devices were removed within the first six months due to hyperplasia. An additional two devices were removed by the second year of follow up due to obstruction and/or irritation. Although the patient numbers drop off, out to three years, an additional five patients had the device removed for similar reasons; i.e., enlarged prostate, hyperplasia or obstruction.

To further elaborate on this, let me present one case that was presented in the PMA.

[Slide.]

This patient developed a rapid growth of prostatic hyperplasia within two years post-insertion. Not only was the gland markedly enlarged compared to the pre-insertion assessment of 40 grams versus 94 grams at removal, but also the prostatic tissue and the mucosa produced severe obstruction. The patient underwent an open prostatectomy.

[Slide.]

Two pathological examinations of the adenoma showed numerous small papillary structures protruding

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through the fenestrations of the stent--you can see the protrusions and the wires into the lumen of the urethra.

[Slide.]

These micrographs illustrate well these changes. As you can see, there is a significant amount of proliferative glandular dystroma, not only the epithelium but the stroma protruding into the lumen.

In view of this being the only case having a complete biopsy of the adenoma and the stent, one is hard-pressed to draw any definite conclusions with respect to device/tissue interaction. However, since 13 other cases with similar proliferations, two having carcinoma and one with atypia, were found on tissue removed by TURP over the limited course of the trial, one is justified to raise a question as to what histological process will take place over a longer period of time.

In conclusion, the device is clearly an option for non-surgical candidates, patients needing immediate relief, patients in poor medical health or very aged patients. However, without an active control for comparison, the risk of irritation, encrustation, tissue ingrowth and device

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removal associated with implanting a foreign body must be looked at very carefully when deciding on the appropriate patient population for this device.

Training on the accurate position of the stent is needed to help minimize some of the risks.

I will now present the charges to the panel.

[Slide.]

The sponsor has proposed to indicate the device for all men with PBH. The patients enrolled in the UroLume study were approximately 70 years or five to ten years older than comparable BPH study cohorts with which we are familiar. Do you believe that the inherent properties of the UroLume and the clinical data support the current broad indications or that a more restrictive target population is appropriate?

No. 2: Based on the information available in the PMA, do you believe that the benefits outweigh the risks for the patient population as defined?

No. 3: Is the information in the physician labeling sufficient to optimize patient selection, counsel patients appropriately and provide adequate instructions for

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use? If not, what additional information should be provided. Please address the following portion of the labeling with respect to accuracy and completeness: indications, contraindications, warnings, precautions, and a summary of clinical results including adverse events.

No. 4: Does the draft patient labeling provide sufficient information to the patient so he can make an informed choice whether or not to use the device? Is the information provided sufficiently comprehensive and understandable to patients so that they can assess the risks and benefits of this device versus other currently available treatment modalities? If not, what additional information should be provided?

No. 5: If approval is recommended, are there issues that need to be expanded upon or clarified in the post-approval studies?

Thank you.

DR. MELMAN: Thank you, Dr. Herrera.

Panel Discussion

What I would like to do now is to ask Dr. Robert DiLoreto to lead off the panel discussion with his review of

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the information that was submitted. He was actually the only primary reviewer of this.

Bob, I would like you to begin.

Primary Reviewer

DR. DiLORETO: I am not going to resummarize the things that have been summarized multiply already today and, in fact, very well by both the FDA and the sponsor. Basically, in summary, though, it is a stent similar to the stent that we approved last year for stricture disease that was being purported for use in patients with BPH.

The study cohort inclusion and exclusion criteria everyone has in front of them. Basically patients older than 45 having low urinary symptoms in need for some sort of intervention with acceptable risk of anaesthesia were the population that was looked at, the hypothesis being, again, the ease and reliability of the use of this stent for BPH, that efficacy in changing the voiding symptoms and voiding function, the follow up and assessment of the epithelialization process and potential effects on the UroLume device and, of course, the safety and efficacy.

Two study groups were looked at, randomized and

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non-randomized. The non-randomized was a total of 144 patients at 13 sites, again the three hypotheses being the increasing peak flow rate, decreased total symptom score and decreased residual urine.

The randomized study was--and I will have to rely on the FDA reviewers--I believe not statistically significant based on the numbers that were present although the patients in the study appeared to have adequate response post-treatment. With that in mind, I think the issues specifically relate to the charges to the panel that Dr. Herrera has just presented.

These are issues that I brought up previously concerning long-term safety, patient age or selection for implantation of this device, issues concerning transitional-cell carcinoma, issues concerning irritative symptoms and issues on how that patient population is excluded or should be excluded from implantation of the device and what needs to occur from the standpoint of post-marketing studies.

Actually, Arnold, I will leave it at that and then just open the floor up to the panel.

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DR. MELMAN: Thank you.

Open Discussion

Why don't we start at the opposite direction. I will ask Dr. Sadler to begin, if you have any comments.

DR. SADLER: As one who spends his career on the other end of the urinary tract, I think I have to be very limited in my comments about technique since I am as likely to have this in my urethra as in my hand. So, as a potential patient, I don't see this as an appealing alternative to everything else that is out there.

I do believe that when we are looking at a population of tens of millions of growing prostates that the experience with less than 150 patients is not enough to give us complete confidence that we know what is going to happen. So I do believe that there should be restrictions on its use.

I think the kinds of restrictions imposed during this study are reasonable. I think further that until more data is obtained, it probably should be restricted to candidates who are higher surgical risk and who are 60 years or older. I think that would avoid doing something in a

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urinary tract that has 30 years to go and might have multiple interventions required to correct something should there be a problem.

I would like to raise just a couple of questions having to do with the documents to go with the device. It says a trained physician and suggests that he watch a video. I would think that the urologic surgeons on our panel would think that that should be somewhat more restrictive.

I consider myself a trained physician but I don't think I should be placing these things. I also think that a video is hardly sufficient training.

The patient brochure is deadly dull and inadequately informative. It needs to be rewritten in a more conversational way with color diagrams that happen to have labels and legends. It is not very informative and places too great a burden on the professionals taking care of the patient to inform and to document their information to the patient. The manufacturer needs to provide a better document.

DR. MELMAN: Let me do it in a different way. I am going to go through the five charges that we have. You

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have actually addressed some of them. But let me do the first one. I will repeat the charges and we will go around the panel in that manner.

The sponsor has proposed to indicate the device for all men with BPH. The patients enrolled in the UroLume study were approximately 70 or five to ten years older than BPH study cohorts with which we are familiar. Do you believe that the inherent properties of the UroLume and the clinical data support the current broad indication or that a more restrictive target population is appropriate?

Let me come back to you. You have already said you thought 60 years of age or older. Do you have any other comments about the population?

DR. SADLER: As I say, 60 years or older, or those who are at higher operative risk since this is a shorter procedure with lesser anesthesia.

DR. MELMAN: Higher risk is very vague. I guess we tend to want to make things more vague so we are not too restrictive, but that is still very vague.

DR. SADLER: In that case, I will leave it to those who have to do the operations to decide whether to put

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it in or leave it out.

DR. JETER: This is redundant, I know, but I just feel compelled as the consumer representative to support Dr. Sadler but to issue a little bit more of a passionate concern. I just remember when Eugene Bricker reintroduced the Bricker loop for treatment of patients with bladder cancer and then it was generalized to young patients. Many of those young patients who had ileal conduits went on to renal failure and dialysis or death.

I, like Dr. Sadler, am very concerned about generalizing this to younger patients where there could be 20, 30 more years where complications could arise.

DR. MELMAN: What would your recommendation be? What would you like to do? We are at the point where we want to make some recommendations.

DR. JETER: I would certainly go upward of 60, more to 70. But age is a relative thing. There are some very young 70-year-olds and there are some very old 60-year-olds. I really think it has to do with the whole total condition of the patient.

DR. MELMAN: But there are actuarial data that we

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know in the population how long someone who is 70 is expected to live in our population.

Any other issues about this first charge?

DR. DiLORETO: Arnold, can I jump in here?

DR. MELMAN: All right.

DR. DiLORETO: I concur with both Katherine and Dr. Sadler that age is, obviously, a variable variable. We could split the difference between the two, but I do think that something has to be mentioned along the lines that this particular group of patients ought to be felt to be a poor risk for standard surgical therapy.

That does not exclude any other forms of non-surgical therapy but that it be limited to that group of "x" age, whatever we decide, 60, 65 or 70 that are at poor risk for standard surgical treatments for prostatic hypertrophy.

DR. HUNTER: This is unusual for me not to agree with everyone but I don't agree with everyone. I have to include into the minutes--Howard Epstein and I know each other from the University of Florida for many years. He trained there and I asked him a question, and you may want

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to respond publicly for the forum so I don't paraphrase it wrong.

But I said, "Who would you use this in?" And Howard basically that he felt like he would use it in anyone after appropriate discussion with the patient. A lot of what we do in life, at least as I get older--90 percent of what I do is based on trust and about 10 percent based on information because it is hard to read statistics and information, although, when things hit the fan, you have to go back to data.

Usually, I am very restrictive but, in this case, I am having some symptoms so I wouldn't want it to be restrictive. I think that the data shows that this device was used when the prostatic urethra was greater than 2.5Êcentimeters, when the gland was moderately small, 40Êgrams or less, when the patient was over 48--I believe it was 48--years old, when there wasn't a significant median lobe, when there weren't irritative symptoms and when there wasn't really a bladder-neck contracture or incontinence, it helped the patient's symptoms and it did a pretty good job.

So I think that it should be approved for that.

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The caveat is we have a small amount of data. We need to follow because of the long-term implications of the transitional-cell mucosa and unknowns. So there needs to be a registry to protect the long-term and continue to follow up for that data.

I am just going to hit the other issues and then I am through, real quick, which is rare for me, also. Training; I think that this is an easy device to use. I think of the things that I have used and do and have had to learn to do, I resent having to review a video and pay $400. We did with Continent materials before.

I think that is ridiculous. I think a video and a physician-information brochure that I sign and goes back to the company and they have a registry that I have read that and I feel comfortable and I can do it, I don't think I need to see anything but a video. I don't think I am exception. I think that I am probably the rule.

Howard mentioned about his residents, and I am sure Joe and our other colleagues would echo that. But I may be in the minority there. So, basically, if you have long-term follow up, I think, with those restrictions, it

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would be fine and I don't see any problem with this device.

DR. MELMAN: Dr. Sadler just commented to me that he thinks he would indicate it should be a urologist not a trained physician. So would you agree to "trained urologist"?

DR. HUNTER: Yes. I would not say anything about board-eligible or board-certified. But I think that you should be a urologist using this device, obviously. You might extend that to "able to handle the complications associated with--"

DR. MELMAN: That would come under "trained urologist."

DR. HUNTER: My only other question was how do you have a registry and long-term follow up which we will answer later, and where should this be done and is there any coding and development and reimbursement being developed. I think the marketplace, long-term, if this device doesn't kill people, and I don't think it does, and it really doesn't harm people, is that the marketplace will decide, long-term, how good the device is and whether it is used or not commercially. Where should it be used and have we got codes

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and reimbursement for this?

DR. EPSTEIN: Howard Epstein speaking. Just to echo what Pat had said. Basically, the first issue is where would I use this stent. In terms of any age restrictions or whatever, I don't feel strongly about that. I feel that this falls in the same line as surgery. Any patient that I would consider for a TUR or a TUNA, a surgical intervention, I would consider the stent.

I think that we go by the symptom scores that come out by the federal guidelines. I think, obviously, if someone is 40 years old and they come in with PBH types of symptoms, the first thing I would do is I would get a urodynamic study and I would do other workups because someone who is 40 is much less likely to have just straightforward BPH than possibly something else going on or some other treatment that may be indicated like a bladder-neck incision.

I do agree you need to follow these patients but it is the same thing like putting in a penile prosthesis or a breast implant or anything like that; you should follow those patients to make sure that they are okay.

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These are an older population of patients in general, not like, say, a stricture patient who could be 30 years old. So I don't think we are going to be talking about 30 years of follow up here in general.

In terms of where I would put this in, there is no question that if you have cystoscopic facilities in your office, you can do this in your office. This is not a hospital procedure. You don't even, necessarily, have to do it in an outpatient facility although that would be another place.

But this, again, just like the TUNA, is easier and it can be done in five, ten minutes in your office under the right conditions.

DR. HUNTER: Fine with me.

DR. MELMAN: Thank you, Dr. Epstein.

DR. JONES: I certainly agree with those that have previously spoken. But I do agree with Dr. Hunter. You certainly have to determine age and your findings of that patient's prostate. Those are the major factors that needed to be done. Even age doesn't always tell us who has the large prostate and I agree with that.

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DR. BENNETT: I really don't think age is an issue. I would eliminate that because I think it would box a urologist into something that they don't really want to be boxed in. I think the issue is non-surgical candidates or patients who refuse surgical therapy. I think that is the critical issue.

Another point is the ease of removal of this device which hasn't been talked about that much is essentially what you were going to anyway, which is a TUR. I think that needs to be considered because it is not a difficult device to take out. You just simply resect the mucosa or clasp the mucosa and take the device out with a grasping forceps, and then you perform what you were going to do in the first place.

So if you think about that, then maybe there should be no restrictions at all on who gets the device and then we are backing what Howard has said. But the age issue, I think, is not an issue. And the other reason the age issue is not an issue is that urologists understand and today they talk to their patients about all kinds of options.

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I think it will just box the doctor into a corner.

DR. MELMAN: I have a little different philosophy. I think as the advisory panel, we want to be able to say that we know that the placement of this device is safe if it is put in at age 45 and you are going to live 30 years. I don't think we can say that because we don't know what the 30-year data is. So that is a problem.

DR. BENNETT: The problem there, Arnold, is really the material. It is an unusual material. It has five or six metals in it. I assume when you approved it, and I was not on the panel nor saw the information on the metals-corrosion testing and whatever on the original material, that that has been dealt with. A lot of these materials are in vascular stents and stents that are used in other applications which stay in forever, also.

That is a different issue when you talk about--

DR. DiLORETO: Arnold, I am missing some of this.

DR. BENNETT: We are just talking about what happens at year ten. I think that that is a materials issue, and what happens to these five or six metals at greater then five years. We have seen some nice pictures

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that go out a couple of years and there is very little inflammatory reaction around the material, itself.

DR. DiLORETO: But, again, there are not any long-term data, experimental or not, to find out exactly what that is. Arnold's comment that the study really is based on an older population group, not the younger population group, maybe that can be resolved with post-marketing surveillance which the company, obviously, has been very good at in the past.

But, again, I think that we have to decide based on the data in front of us and the bulk of that data is an older-age population group.

DR. OESTERLING: Joe Oesterling speaking. The only two additional comments that I might make would be one, that about 45 to 47 percent of the patients in our study group were under the age of 70 so we do have a fair population of less than 70 years of age. The second thing, if I remember correctly when we had approval for the stricture application, the age limit was 30 years.

So we went way down for putting this exact same device in for the stricture application, in fact all the way

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down to the age of 30.

DR. MELMAN: But with the urethral strictures, the options were more limited than they are for this treatment. I am not sure that this shouldn't be done in labeling, and kind of just let the buyer beware, the patient be told what the long-term follow up are and then they can decide.

The other thing is that I am not sure that this should be put in in the presence of a transitional-cell carcinoma of the bladder when you get these polyploid extrusions that I think might be very difficult to differentiate from a new tumor. I think that should be a restriction until we have more information so that people who have bladder tumors or CIS of the bladder, this device should not be put in those patients.

DR. BENNETT: I would concur.

DR. HUNTER: I agree.

DR. SADLER: I agree.

DR. MELMAN: The other was that the AMS, itself, through their experts, said that this device wasn't any better in treating patients whose predominant problems were irritative symptoms. In other words, there was no

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statistical difference in removing the symptoms of urgency, frequency, nocturia.

DR. HUNTER: And incontinence.

DR. MELMAN: And incontinence. So I am not sure those symptoms, by themselves, should be an indication for putting in the device. You would like to speak to that issue.

MS. BURNSIDE: Diane Burnside, AMS. I believe what we said is that they were statistically significant but I believe the physicians were saying they weren't sure how clinically significant those changes were for irritative symptoms.

DR. MELMAN: Again, that might be handled in the labeling and that is that should be put in the labeling. I think the market will determine--urologists are not going to put this device into people who primarily have urgency. I don't think we have to tell people they shouldn't, but--

DR. BENNETT: I think what you were saying, Arnold, is true for TURP, also. So the patients whose primary irritative complaints for TURP don't do as well as the patients who--

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DR. MELMAN: That's correct.

DR. SADLER: As a non-urologist, I would say I looked at the data and saw that it didn't make incontinence or irritation worse. That, to me, was as good as I could have expected considering what they were doing.

DR. MELMAN: You want to try and make it better. A trained urologist wants to make it better.

DR. SADLER: A urologist will make it better but a stent won't make it better.

DR. MELMAN: We will talk about the recommendations later. Now let's go to item no. 2 which is, Based on the information available in the PMA, do you believe that the benefits outweigh the risks for the patient populations as defined? Dr. Bennett, would you like to comment on that?

DR. BENNETT: No comments. I would agree with that.

DR. JONES: I do, too.

DR. HUNTER: Yes.

DR. JETER: No comments.

DR. SADLER: The population, as studied, not as

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defined. I don't know about the population as defined.

DR. MELMAN: So it is yes to the study population.

No. 3. I don't think we have any objection to that. Is the information in the physicians labeling sufficient to optimize patient selection, counsel patients appropriately and provide adequate instructions for use? Please address the following portions of the labeling with respect to accuracy and completeness: indications, contraindications, warnings, precautions, and summary of clinical results including adverse events.

Dr. Bennett, you said you had some comments about this.

DR. BENNETT: I was not privy to the labeling because of my position of industrial rep. So all I had was a summary of the clinical material. So I am unable to comment on that.

DR. JONES: I really believe that patients should have that type of information before they have this stent put in or have the options for it, for other types of options.

DR. HUNTER: I think that the information could be

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improved. I do think that you definitely need to have it and I would like to see the patient get something also before they could have the procedure.

DR. DiLORETO: Arnold, I'm sorry. Are we talking about 3 or 4?

DR. MELMAN: 3.

DR. DiLORETO: So this is the physicians labeling, not the patient labeling.

DR. HUNTER: Right. But I think the physicians labeling could be improved. We can elaborate much, much later but I think it needs to be improved.

DR. JETER: I do, too. I agree with that.

DR. SADLER: Yes. I thought it was inadequately clear that the kind of exclusions that were used in this study were recommended exclusions for patients to use it. You have said that if they have a large median lobe it doesn't seem to work very well. That is not really clear from the warnings in the physician instructions--and I think the similar exclusions for malignancies and infections and instrumentation recently are valid.

I will trust Pat and the other urologists'

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judgments as to what training and background is needed. I do believe that it should specify the urologist should do this and I think that the exclusionary criteria should be explicit. I think the data is going to have to be collected.

DR. DiLORETO: I would concur. Again, being a little bit more specific assuming we agreed on the transitional-cell carcinoma group and also emphasizing--albeit I know the urologists won't do it, but emphasizing the issue of the patients with irritative symptoms. I don't know if we came to a final conclusion on Point 1 but, obviously, patient age and whether or not this be recommended to be used in patients that were considered poor risks for formal surgical treatment and, if we did do that, that should be in there.

DR. MELMAN: We didn't decide about age. We are divided.

DR. DiLORETO: No; I mean whatever the final decision is, obviously that needs to be placed in this section.

DR. MELMAN: Let me come back to age since we seem

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to be--Dr. Jones, as the oldest member of the panel, let me ask you to talk about that.

DR. JONES: I have no comments about that right now.

DR. MELMAN: That is punting. I think we have to make a decision.

DR. HUNTER: If you had to pick an age, what age would it be?

DR. JONES: Oh; to pick an age?

DR. HUNTER: Yes.

DR. JONES: I would feel that if it is over 65, and after you cystoscope, that should be the two major things that need to be done to determine whether or not they are going to need a stent or not.

DR. MELMAN: Can I infer from that that you would not recommend the placement of a stent in someone who is under 65 years of age today, until we have more long-term data. Is that what you are saying?

DR. JONES: I can't say that, but I never did. I never did a stent. I said I always treated with Hytrin.

DR. MELMAN: Dr. Bennett, you would not put any

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age restrictions?

DR. BENNETT: I would not put any age restrictions. You could have a 59-year-old man who needs a stent or who is obstructed who has had five bypasses and is in mild congestive failure and his life-expectancy is going to two years and he will get the world of benefit out of a stent. So I think you are putting the urologist and the patient's physician in a box by putting an age on it.

DR. MELMAN: To the FDA, whoever wants to speak for the FDA position, since there is no long-term data beyond four years or five years, is it sufficient to put in the labeling that the patient can read that there isn't that and we should consider that when considering having this procedure done and leave it at that so we don't have to recommend an age restriction.

MR. GATLING: You have two issues here. One is about the long-term data and the other issue I hear is the actual age when the device might be recommended for use. I think that is something that we need to get back from the panel--

DR. DiLORETO: Excuse me. Speak up, please.

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MR. GATLING: Okay. What you need to do is look at the age of the study population and decide whether you can infer younger populations from that. If you feel that you don't have enough data at this particular point in time, you may want to have another study to look at that younger population.

It would be good if you could give us some guidance on the age group that you are thinking this is more appropriate in. It could be based on the study at this point in time.

DR. MELMAN: I don't think that is what we are saying. We are not saying that it is going to be less efficacious in someone who is younger. What we are saying is that we don't know that in ten or fifteen years there may not be complications that are unanticipated that you can't pick out now.

What Dr. Bennett is saying is, why should you restrict it to someone who is 50 who has had 3 MIs, who has diabetes, really couldn't tolerate an operation in whom it would work. That is the conundrum that we are--

DR. DiLORETO: Arnold, that could be covered by

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making a statement that we come up with an age but that is not the--the recommendation is patients above this age and/or patients that have even less than this age medical conditions that would preclude or make conventional modes of therapy risky, and that that would then open the door for that particular group that Dr. Bennett had mentioned to have this particular product inserted. You don't have to limit it just based--

DR. BENNETT: Another way to look at it would be to say for patients whose life expectancy is not expected to exceed five years. That is another way of looking at it and forgetting about the age issue.

MR. GATLING: Another way you can do it, and how we have done things in the past, is you, basically, present in the labeling the kinds of study results that were obtained in the actual study and just say that we don't really know what the long-term effects will be.

DR. MELMAN: That is what I asking, if that would be--

MR. GATLING: Yes; you can do that.

DR. DiLORETO: I'm sorry; I didn't hear, Bob.

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MR. GATLING: Basically, what you can do in the labeling is that you can indicate the type of information that was actually collected in the clinical study and, if you have other concerns that you don't really know the answer, just say that, that we don't know about the long-term effects or we don't know about--

DR. DiLORETO: I think that would be reasonable.

DR. SADLER: My point is simply that if you say this should not ordinarily be used in someone under 60 years of age, their insurance is still going to pay for it if they are 58. The urologists are going to use it where they want to. There is no reason not to recommend that because the data is not there that this would ordinarily be used in people older.

I don't see it as something that ought to be absolute. I agree with Dr. Bennett that you should not put a doctor in a box where he can't get out, he doesn't have any options. But I think that the information should be explicit, that we have short follow up on a small number of patients and the long-term prospects are unknown.

I think we have to say they are unknown. We are

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putting a foreign body into the urinary tract indefinitely and we don't really know what is going to happen. I have no expectation that some catastrophe is going to follow doing this but I have no confidence on which to say that except just a guess from my knowledge of materials and procedures. But I have great reservations about putting foreign bodies into people and I think this is putting one into an area that does have some liability for infection, particularly with people who have prostate disease and who have had partial obstruction.

So I think that we have an obligation to say we don't know and that we don't have a basis for recommending its use in circumstances where there is a high likelihood of long experience. I don't want to put an absolute restriction. I don't mean to say that. I mean to give very explicit advice, however.

DR. MELMAN: So you would not put a specific age but that would be part of the labeling that would be highlighted that both the patient and the physician would look at?

DR. SADLER: I can't emphasize too strongly that

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we have data on fewer than 150 patients and only about 25 of them got to the four-year point. Most of them, the data stops after about two years. And that is reasonable for a study like this. But we can't infer from that data what is going to happen when this is done on a half a million men.

DR. MELMAN: To be the devil's advocate, why not say at this time that you would restrict it to people who are over 65 and do further outcome of long-term efficacy, with some exceptions.

DR. SADLER: I think that there needs to be an opportunity for justification of exceptions. But when a doctor does something and creates an exception, he has to be accountable for that. He has to stand up for it. That is all I am saying. If that is what we want to do by saying it should not be used in people under 60, then we could say that. But I think that advising them explicitly of the reasons for that as a recommendation puts the onus right where it belongs, on the physician who makes the decision and I am willing to accept that.

DR. MELMAN: So what I am trying to get from you is would you give an age limit? Would you say over 60?

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That is what you did in the beginning.

DR. SADLER: I think 60 is a reasonable boundary for that recommendation.

DR. BENNETT: I think this is a very unusual precedent. Except for pregnant women and children, I can't think of any device that has been restricted to an age. Having had a lot of experience with CPT coding and relative values, I can just see what is going to happen.

DR. MELMAN: Mr. Gatling pointed to his eye when you said that.

DR. BENNETT: Is there? I am going to get educated here.

DR. DiLORETO: Howard, could you have Dr. Bennett just restate that? I missed that.

DR. BENNETT: I may not have to, Bob.

MR. GATLING: This is Bob Gatling. I think the main thing I have ever seen on age limit had to do with intraocular lenses, mainly. A lot of it had to do with one, the dataset that they have, plus the life expectancy of that product.

DR. MELMAN: What has happened with that as there

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has been more experience?

MR. GATLING: As far as I know, there is still an age limit on that.

DR. MELMAN: What age was decided upon?

MR. GATLING: I believe it is 60 years old. I believe that is what it is.

DR. DiLORETO: Didn't we put an age limit on the wall stent?

DR. MELMAN: I think it was over 30.

DR. BENNETT: That was more related to the lens degrading--

DR. DiLORETO: I'm sorry; I am missing that.

DR. BENNETT: Wasn't that more related to the material, knowledge about the material, how long it would last as far as the eye?

DR. DiLORETO: No; if I remember correctly, I thought one of the main concerns at that panel meeting was something that we are discussing today, which was, in fact, the length of time that these implantable products potentially could be present, and that we looked at setting an age threshold. Actually, I believe there was another

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threshold saying that they had failed other modes of therapy.

But the concern at that time was the long-term effects of leaving an implantable device in, which I suspect is the same thing we are talking about right now.

DR. MELMAN: Let me just go around the panel again. I want people to get off the fence. Dr. Bennett, do you want to have an age limit?

DR. BENNETT: No age.

DR. JONES: I think it is the patient, that we should find out, whatever his age is, the size of the prostate that we need to put it in and any other complications the patient has. I think those are major factors.

DR. MELMAN: So that is a no. I am translating that as a no.

DR. HUNTER: In the past, we have taken the data to use--at least we have some data on this age population. So if I were to restrict age categories, I would do it based on data that we have. I am 45. I would like to have the age restriction lowered to 45. But the study was 45. 45 to

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50, I think, is a reasonable age. I don't think there is any difference.

The long-term thing, we are going to identify and keep. We are going to have somebody follow five and ten years out, some sort of registry. I don't think there is a difference in a 45-year-old, ten years later, getting a cancer and having a problem or some serious problem than there is a 60-year-old guy when he is 75 having it.

He still has a bad problem so I don't think an age restriction really protects people from that and I don't think that is a reason to restrict it. We do have 30-year-old patients with these in them for stricture disease.

The material, I think, of surgical clips and surgical wires in people in their brains and other places, this usually is covered. So I don't have a problem with it. I think if you want to do an age restriction, use what the data has supported. If you don't, then you don't need to. Don't pick some arbitrary thing.

The long-term follow-up data should be either a registry or something like we do always in our post-approval

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studies to follow out those bad things that might happen that probably won't.

DR. JETER: I don't like to disagree with you. I think that the age--it either ought to be life expectation or it ought to be the age of those in the study, those who were studied.

DR. SADLER: I still believe that it would be wise to say patients should ordinarily be over 60. I believe that a line can be put in to say that justification can be provided for exceptions.

DR. DiLORETO: Listening to both sides, I am still concerned. I would concur with Dr. Sadler and leave the opening for patients under that age. I am quite concerned, though, still, that if you just open it up to over the age of 45 that the onus is, hopefully, on responsible physicians and that this would be put in not de novo; they failed other modes of therapy, can't take medications or potentially can't have an operative procedure.

But, unfortunately, past experiences have led me to believe that, depending upon marketing and patient information, et cetera, this could end up being a highly

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used and potentially abused mode of therapy.

I would concur that we limit it to 60 but then leave some wide-open language for the exceptions under that and that could be developed with the panel's help and the FDA personnel along with the company at some other session other than today.

DR. MELMAN: So there are two people who have voted no age restriction, two people who have voted to limit it to the age that was used in the study, and two people who have voted for an age-60 limitation. I am going to throw my vote in with that lot, with leaving it open so that people who are younger who have medical indications can use it, which I think makes it pretty broad.

The fourth issue is, Does the draft labeling provide sufficient information to the patient so that he can make an informed choice whether or not to use the device? Is the information provided sufficiently comprehensive and understandable to patients so they can assess the risks and benefits of this device versus other currently available treatment modalities and, if not, what additional information should be provided?

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Dr. Jeter, I will ask you to address that first.

DR. JETER: Thank you very much. I agree with Dr. Sadler. The patient information leaflet as it is is not acceptable. First of all, there is talk about a medical-information card. I certainly think that if the patient is not to be instrumented, then the patient ought to be wearing a bracelet.

The wording is certainly not at the seventh grade or below level. It is way up in the college level. I certainly don't think that a great deal of wording needs to be devoted to the insertion tool. A patient isn't given a great deal of information about various scalpels, scopes and other things in other procedures.

I think that is very confusing. A little bit of information is fine but I don't think that needs to be belabored. I think there are things about bicycles and horses and pain and that sort of thing that, if they are in there, it needs to be much more specific or the patient and the patient's family will become very concerned.

It says, "Because physical manipulation of the UroLume Prosthesis may cause pain or movement of the

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prosthesis, you should avoid applying unnecessary pressure to the area where the prosthesis is located." Well, that is very confusing to a patient. When the prosthesis is inside the body, how could you apply pressure up there inside?

Are you talking about behind the scrotum? The patient will not be able to understand inside the body and outside the body. Certainly, there need to be a number of illustrations. And then such things in the glossary of terms; a suprapubic catheter is described as a catheter placed through the stomach. That is not acceptable. And anesthesia is described as the loss of all sensation in a specific area of the body.

A patient understands anesthesia as being put to sleep and not losing all sensation. Somebody needs to start over again.

DR. SADLER: In other words, Dr. Jeter and I volunteer to edit.

DR. MELMAN: I just wanted to clarify. AMS is not suggesting that the patient can't be instrumented in the future. It is just in the first few days after--

DR. JETER: But still, in all, this is something

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that they said could be done in the office, theoretically, in the patient.

DR. MELMAN: No; I mean, after the placement of the prosthesis they could then later undergo cystoscopy or catheter placement.

DR. JETER: I understand that. But what I am saying is that even in that first month, if this is just a short, uncomplicated procedure as had been described, then theoretically, the patient could fly off to New York or from Michigan or from anyplace else. There is a time frame there where I would think the patient would be vulnerable to other accidents or illnesses in which it would not be a good time to instrument the patient.

DR. SADLER: I think I have already said my piece about the patient information brochure. It just simply needs to be done over. It is insufficiently illustrated, insufficiently conversational and not entirely accurate.

DR. HUNTER: I think they can edit it perfectly. It does need to be changed. I would like to have the MS rep provide me with a videotape and a little card saying that I have been trained or have read it. I would like some

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patient-information things that I can give to them, one page, preferably and then, if they want more, they get it somehow.

DR. MELMAN: As an aside, I have to say that most of the patient information booklets are in the box. They come along with the box that you have in the operating room. That is all the companies. There has not really been an effort to make sure we have those booklets in our offices. At least, I don't have them and I suspect I am not alone.

I think the companies should make more effort to have those booklets sent to the practitioners.

DR. HUNTER: A patient video and a handout. I really think that is important.

DR. SADLER: This is enough different from what patients usually encounter that they need something that illustrates it, too.

DR. MELMAN: It is true for this and for other devices, also.

Dr. Jones, any other comments?

DR. JONES: My major comment is that we need to know about a patient, what his problems are and his age, the

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size of the prostate. These are three points that I feel that the patient needs to have.

DR. MELMAN: This is just about the patient-information booklet, though. Do you have any comments about, in addition to--

DR. JONES: I agree with Dr. Hunter, that they ought to have a video and they ought to have a book.

DR. BENNETT: Dr. Bennett says he agrees.

Any other issues that anyone would like to address?

DR. SADLER: Dr. Hunter has made the comment that there should be a registry or some sort of follow up. I don't know whether we want to specify what it should be or whether AMS should tell us what they have in mind. Obviously, if they don't do it, someone else may and it may turn to their detriment if they don't.

MS. PRITCHARD: Lisa Pritchard with American Medical Systems. What we would plan to do for this device is the same as what we do with our penile prostheses, the artificial sphincter and the stricture application of the UroLume, and that is, with all of our devices, we have a

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patient-information form that is--

DR. DiLORETO: I'm sorry; could you speak up, please.

MS. PRITCHARD: Certainly. We have a patient-information form that goes out with all of our devices that is completed to provide us with information on the patient, the device that they have received, so that we can maintain a record of all patients, what they have got and we are able to follow them through that system that has worked quite well for us.

DR. SADLER: I don't think that is quite specific enough. I really think that there ought to be a specific program to contact people several years after this is done so that data will be acquired. You can do that by giving Dr. Oesterling or somebody a grant to do it, or you could follow all your patients.

But whether it is a sample or the population at large, I think somebody needs to acquire some long-term data and it is in the company's interest to do that.

DR. OESTERLING: I agree with what has been said here in that we need to follow our patients in a careful way

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so that we know what is happening ten, fifteen years down the road. What we have done with the patients who have gotten this device for the stricture application is that we are following them for a total of ten years.

They come back every other year, or biannually, and get a cystoscopic examination. Then, on the fifth year after placement, a biopsy is done. We all thought that that was reasonable when we were talking about the stricture application. That situation is in progress and we are doing our very best to get all those patients back in in a compliant way.

But, having said that, it is a bit difficult. Many of these people don't want to be bothered. They don't want to come back in. They don't want to be instrumented again. But we are certainly doing the best we can.

DR. MELMAN: Any other comments?

DR. SADLER: No; I think my point is clear.

DR. MELMAN: We have to make a recommendation. How would you like the registry to be done?

DR. HUNTER: You have a patient database, so, at five years and at ten years, you send them a post card and

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say, "Go see your doctor and have something done," number one. Number two, if they turn up in the emergency room and something happens, there may be a way, indirectly, of getting information back to the company as to the device extruding, and so forth, like we do with implants.

We know to send it back and contact the local rep and he gets it back to company. Other than that, I don't know how you would get long-term follow-up data. It is hard to mandate. Patients move and so forth and older patients will die or move to Florida and then I will have them all.

But I think a postcard notification at five and ten years might be something reasonable to do with device if you are worried about long-term complications. Like the car dealers do. They send you something in the mail. It is up to you, then, to go get it fixed. If you don't and you have a wreck, you can't sue them.

DR. MELMAN: But that is not going to help the long-term data collection. That is the problem. I recently had a patient who had had a coronary-artery bypass. He presented to me a little plasticized card that actually had a diagram of which vessels were operated on with the

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physician's name on the other side.

I think that is a good idea. That is something, in fact, I was going to adopt for penile implants.

DR. BENNETT: If you get a coronary stent, you get a little plastic card that goes in your back pocket that says you have a coronary stent. For this, because the urologist who sees this patient three or four years later and might have to do a TUR, I would certainly want to know that that patient had a stent.

We don't all do X-rays on patients before TURs to see this metal stent in there. So there has got to be some knowledge that this patient has had a stent.

DR. MELMAN: One of the questions is whether we should make this a recommendation.

DR. HUNTER: I hate to say this, people aren't cars, but like you do with the car thing, you take that to your dealer, he examines you and he fills it out and he sends it back in to the company. Then the company has some data. You may only get 10 percent hits or less using an internet expression but that is better five- and ten-year data than we have now.

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Otherwise, somebody has to come up with money and follow these patients at a study site somewhere.

DR. DiLORETO: Arnold, isn't there also--maybe the FDA people can comment--a standard policy for adverse effects or adverse outcomes that requires some sort of reporting? I am not sure exactly how it functions, but could this not also be used in this avenue?

DR. MELMAN: During the study, there is an adverse form. But this is now--

DR. DiLORETO: No; I mean with post-marketing. I have seen in hospitals posted in the OR and other places, and I think there is an FDA bulletin that comes out with, in it, a back page that physicians or healthcare workers can fill out and send back. It is not specific to anything. It is just in general for adverse outcomes, adverse effects for drugs or products. Somehow, that element of a registry can be tied into this.

MR. GATLING: There are a couple of things here that you can address. What you are referring to there is the MedWatch Program that we have user experience and we can get it back into our system.

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DR. DiLORETO: Bob, can you speak up?

MR. GATLING: I am trying to speak as loud as I can. The MedWatch Program is available and that is what the clinicians and the facilities use a lot for us. The manufacturers have another procedure which is the mandatory device reporting and we get information back that way.

The other thing that you are asking about is the long-term complications which we don't know at this point because we don't have the patients out there. We can follow up, as you are saying, as a registry on the current patients that were in the study. But, also, is there any information that you actually want to collect prospectively, decide ahead of time, on either the patients that were already enrolled or in a small cohort?

That is something that we would like to have from the panel. I think that is question No. 5 on the charge as to whether you want to actually have a study done to collect that information or you just want to follow the patients is something we really want to get from you.

DR. SADLER: All I was going to say is if you do what Dr. Hunter suggests, you make an assumption that those

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who don't answer are either doing fine and have no problem or they are dead, or you didn't reach them. So you have a skewed follow up. You don't have an appropriate sampling but you will have something. I think that is reasonable. I think, in terms of a prospective study with specific data, that we don't need to burden the company with that.

If it turns out that this experience needs that, there will be groups of urologists doing it.

DR. MELMAN: What about the recommendation of having a card supplied?

[Affirmative responses.]

DR. MELMAN: The question that Dr. Gatling asked was a different one, and that is is there other information that we feel we would like that they haven't gathered or at least talked about gathering that we think is necessary with this device?

MS. PRITCHARD: Lisa Pritchard, again. I would just like to speak to your card idea. I would like to point out that we do have that currently for the stricture application and there was a draft of that in the labeling materials that we have submitted. The only exception with

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the cards that have been discussed is ours is paper, not plastic. It is a nice, heavy paper.

DR. SADLER: It should be a little wallet card.

DR. MELMAN: It should be a wallet card that has plastic.

MS. PRITCHARD: It is a wallet card. It is a very heavy paper.

DR. MELMAN: Despite your reticence, we are going to recommend that it has vinyl on it.

Does anyone have anything else that they feel should be done? Is this enough? I think the answer to your question is we think what was looked at was complete. We wouldn't recommend any other prospective study for this.

I guess only urinary cytologies might be something but I think we are not going to add that.

It is 12:30. We are going to take a 45-minute break. We will resume at a quarter after 1:00 and we will complete the session.

[Whereupon, at 12:30 p.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

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A F T E R N O O N P R O C E E D I N G S

[1:20 p.m.]

DR. MELMAN: Dr. DiLoreto was supposed to give the summary but, because he is in Detroit, we have decided that I will just summarize what we decided about the five charges to the panel.

The first charge was that we think, as a group, that this device, AMS UroLume device, is indicated in men who suffer from urinary-outlet obstruction and who have prostates that are larger than 2.5 centimeters in length, who are more than 60 years of age or in patients whose medical condition precludes standard surgical therapy.

The device is not indicated in patients who have large middle lobes or transitional-cell--that is, urothelial--cancers or prostate cancers.

We believe that the benefits do outweigh the risks. We believe, in consultation with the company, that both the information given to the physician and to the patients has to be reworked, in terms of the draft labeling.

We believe that there should be some post-approval--if we approve it, there should be studies

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that are done on the patients who have already been entered into the study and that they should probably be followed indefinitely as long as they survive and the company can track them down, that at least in five and ten years after placement of the device that the patients should undergo cystoscopy and cold-cup biopsy of the tissue that is in the prostatic urethra in addition to the studies that have already been done as part of entry into the study which should be continued.

Before we entertain a motion recommending an action on this PMA, Mary will remind the panel of our responsibilities in reviewing today's premarket approval application and of the voting options that are available to us.

MS. CORNELIUS: Thank you, Dr. Melman. Before you vote on a recommendation, please remember that each PMA has to stand on its own merit. Your recommendation must be supported by data in the application or by publicly available information. You may not consider information from other PMAs in reaching your decision.

Your recommendation may be one of the following.

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You may recommend approval of the PMA. You may recommend that the PMA be found approvable subject to specific conditions such as resolution of clearly defined deficiencies cited by you or the FDA staff.

Examples could include resolution of questions concerning some of the data or changes in the draft labeling. You may conclude that the post-approval requirements should be imposed as a condition of approval. These conditions may include a continuing evaluation of the device and the submission of periodic reports.

If you believe such recommendations are necessary, then your recommendation should address the following points; the reason or purpose for the post-approval requirement, the number of patients to be evaluated and the reports required to be submitted.

You may recommend that the PMA is not approvable. Of the five reasons that the Act specifics in Section 515(b)(2), Sections (A) through (E), three are applicable. The data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the labeling.

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To clarify the definition of safe, there is a reasonable assurance that the device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health from the use of device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.

The data do not provide reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling. The definition of effectiveness is as follows: there is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The PMA may be denied approval if, based on a fair evaluation of all the material facts, the proposed labeling is false or misleading.

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If you make a non-approvable recommendation for any of these stated reasons, we request that you identify the measures you believe are necessary or the steps that should be undertaken to place the application in an approvable form. This may include further research.

DR. MELMAN: We will now consider the panel's report and recommendations concerning approval of the UroLume P920023, Supplement 1, together with the reasons or recommendations as required by Section 515, Part (c)(2), of the Act.

The underlying data supporting a recommendation consists of information and data set forth in the application itself, the written summaries prepared by the FDA staff, the presentations made to the panel and the discussions held during the panel meeting which are set forth in the transcript.

The recommendation of the panel may be approval, approval with conditions that are to be met by the applicant, or denial of approval.

I would like to please have a motion.

DR. SADLER: I move it be approved with

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conditions, those conditions to be those outlined in your summary at the beginning of this discussion. Those should be on the indications and the modification of the labeling to the physician and labeling for the patient and post-market follow up of patients, and I believe that that should include 10 percent of patients, if possible, because I expect this would be a large group of patients.

DR. MELMAN: 10 percent of the patients who then have--

DR. SADLER: Have follow up at five and ten years, at no less than ten years.

DR. MELMAN: Do we have a second?

DR. DiLORETO: I will second.

DR. MELMAN: So we have a recommendation of approval with conditions. The conditions are, again, that this should be done in men who have obstructive symptoms, urinary symptoms, are over 60 years of age, unless they have a medical condition that precludes standard surgical therapy. It is not indicated in patients with large middle lobes or urethral prostatic cancers.

DR. HUNTER: What about urethras less than

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2.5Êcentimeters?

DR. MELMAN: And urethras less than 2.5 centimeters. We recommend, as just stated, that the improvement in both the labeling done for physicians and for patient in terms of--also, I would like to add that, as part of the follow up, that the patients be supplied with a vinyl-covered card that they could track around stating what procedure they had, perhaps with the physician's name and AMS's name on one side.

In addition to that, we would recommend that the patients who previously have been entered into the study be followed for life, that they restudied at five and ten years, with the studies that have been previously done and repeated, that they undergo cystoscopy at those two times when they have cold-cup biopsy of their prostatic urethral epithelium, and that at least 10 percent of the patients who undergo placement over the next several years, that they also be followed five to ten years.

I guess it is time for a vote. Will those voting members in favor of approval with the conditions that have been outlined raise their hands?

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[Show of hands.]

DR. DiLORETO: My hand is raised.

DR. MELMAN: So those approving are Dr. Jones, Dr. Patrick Hunter, Dr. Katherine Jeter--

DR. JETER: No; I am not a voting member.

DR. MELMAN: Dr. Sadler, Dr. Robert DiLoreto and myself. That is everyone. So this is a unanimous vote.

We recommended that the conditional approval--I am not going to repeat those again. Does anyone have any questions about the conditional approval?

MS. PRITCHARD: Could we ask a question?

DR. MELMAN: Sure.

MS. PRITCHARD: Lisa Pritchard with AMS, again. We were just wondering if you could clarify the type of follow up that you are looking for on those patients.

DR. MELMAN: The type of follow up? Basically, we would like you to do what you have already done; that is, the studies that have been done in terms of symptom score, uroflows, the things that you have done already. But we have added two additional features and that is five- and ten-year cystoscopy and biopsy of the transitional

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epithelium of the prostatic urethra. Everything else would be the same.

MS. BURNSIDE: What about the 10 percent that was brought in? That was a question.

DR. SADLER: I said that you should do this on 10Êpercent of the patients knowing that you probably can't track 90 percent of the patients for ten years.

MS. BURNSIDE: Of our existing patients on study.

DR. SADLER: I think that what we should say is that your existing patients are too small a population, that this population should certainly be no less than 1,000 patients because you are probably going to have this device installed in 100,000.

MS. BURNSIDE: So what would you like tracked on those, on that 10 percent patients?

DR. SADLER: We are principally concerned about that five- and ten-year follow up, not so much about intermediate short-term follow up, but to really see what happens at five and ten years.

DR. JONES: One question. Will there be any other studies, randomized studies, done on this issue for a longer

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time?

DR. SADLER: Not as the responsibility of company. We haven't recommended that the company do it.

DR. MELMAN: What randomized studies?

DR. JONES: The same study that has been done for the four years that we have.

DR. MELMAN: No; I think we are just basically asking them to continue what they got.

DR. JONES: Continue it on, sure. But I am just wondering if there would be any other studies.

DR. MELMAN: These are points of clarification. We have already voted unanimously for this.

MS. BURNSIDE: I have one more question.

DR. MELMAN: Yes.

MS. BURNSIDE: That is 10 percent within a year of those that are put on, or where does the 10 percent come from?

DR. HUNTER: You want a number? Do you want to just specify a number?

DR. SADLER: We want ten-year follow up on a minimum of 1,000 patients. Let's say it that way. Okay?

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And you can do that starting at whatever point you are able to do that effectively. We know that it is going to be a minority of the people who receive the device.

DR. HUNTER: At that five- and ten-year follow up, you want a symptom score, a cystoscopy and biopsy, those three things; is that right?

DR. MELMAN: No. I think we just restricted it to cystoscopy--

DR. HUNTER: On the 1,000 patients.

DR. MELMAN: Yes.

DR. HUNTER: No symptom scores.

DR. MELMAN: The symptom scores weren't any different.

DR. McINTYRE: Mark McIntyre, American Medical Systems. I would just like to follow up on the 1,000 patients. I wonder if you would find it acceptable if we were to work out a--

DR. DiLORETO: Mark, could you speak up. I can't hear you.

DR. McINTYRE: All right. I wonder if you would find it acceptable if we were to work out a statistical

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sample with the FDA in the following period?

DR. SADLER: Certainly. I think any valid scientific basis would be acceptable to the panel.

DR. MELMAN: I think that we were just concerned, since are clarifying, that the numbers were small and we wanted to ensure, over an extended period of time, there were no adverse effects.

DR. DiLORETO: Arnold, I think that probably could be handled in committee with the company and FDA statisticians and representatives with the aid of selected panel members if they felt they needed to talk to us, but that the specifics of what "n" is and what needs to be looked at specifically could be decided later.

DR. MELMAN: We agree. Any other comments?

DR. HUNTER: I just wanted to clarify a comment in the discussion I made reference to. I talked to Dr. Howard Epstein here at this meeting, just prior to the meeting, and then I asked him those same questions during the meeting so it would be part of the public record. I wanted to make that clear that, in fact, I didn't even know he was going to be here or didn't even know he was part of this study until

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today's meeting. I didn't want there to be any confusion that I had any prior conceived notions and discussions with him at all. Just for the record. Thank you.

DR. MELMAN: Then this concludes the reported recommendations of the panel on PMA P920023, Supplement 1. On behalf of the FDA, I would like to thank the entire panel.

The meeting is adjourned.

[Whereupon, at 1:40 p.m., the proceedings were adjourned.]